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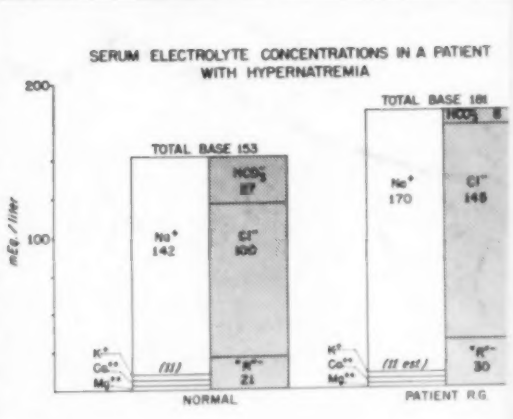

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A.M.A. Journal OF
DISEASES of CHILDREN

Essential Hypertension in Infancy and Childhood

Differential Diagnosis and Therapy

ROBERT J. HAGGERTY, M.D.
MARGARET W. MARONEY, M.D.
and
ALEXANDER S. NADAS, M.D., Boston

Introduction

Essential hypertension is the principal cause of persistently elevated blood pressure in adults.[1] In children, by contrast, essential hypertension is rare; renal diseases, diseases of the central nervous system, coarctation of the aorta, and endocrine disturbances are the commonest etiological factors.*

In view of the paucity of reported cases of essential hypertension in the pediatric literature, it seemed worthwhile to present the cases with this condition encountered at the Children's Medical Center, Boston. We shall emphasize the salient points in differential diagnosis and discuss the therapeutic approaches.

Submitted for publication June 21, 1956; accepted July 25.

From the Department of Pediatrics, Harvard Medical School, and The Children's Medical Center. Assistant in Pediatrics, Harvard Medical School, Assistant Physician, Children's Hospital (Dr. Haggerty); Formerly Fellow in Cardiology, Children's Hospital (Dr. Maroney); Assistant Clinical Professor of Pediatrics, Harvard Medical School; Cardiologist, Children's Hospital, Physician, Sharon Cardiovascular Unit, Children's Medical Center (Dr. Nadas). Supported in part by The Recess Commission on Hypertension of The Massachusetts State Legislature.

* References 2-4.

Material and Methods

The accepted limits of normal blood pressure in infancy and childhood are not as clearly defined as in adults because of (a) the frequent lack of patient cooperation, especially in the infant group, (b) the need for varying cuff sizes for varying sized limbs, and (c) the increase in both systolic and diastolic pressure throughout the growth period. Nevertheless, on the basis of a few accurate series,† norms for children have been established and the correct cuff width for variously sized children has been determined (tables 1 and 2). Generally blood pressure is lower in children than in adults and approaches adult levels at puberty. For purposes of simplicity we have accepted, on the basis of the literature cited, a persistent systolic blood pressure of 130 mm. of mercury and a diastolic pressure of 90 mm. of mercury as representing the upper limits of normal. These levels, it is to be noted, are higher at most ages than the two standard deviation ranges listed in Table 1 and therefore clearly represent abnormal levels.

All of our patients had hypertension by these standards. We have considered the hypertension to be essential in nature by exclusion, if, after exhaustive search, no well-defined cause for it was found (Table 3).

The nine patients forming the basis of this report represent all the children of age 14 years and under with this condition available to us after a careful survey of our hospital records of the past 15 years (1940-1954). All have been studied by the staff of The Children's Medical Center and all but one (Patient 5) have been seen by at least one of the authors.

† References 5-11.

TABLE 1.—*Normal Blood Pressure for Various Ages*
Adapted from Data in the Literature
(Figures Have Been Rounded Off to Nearest Decimal Place)

Ages	Mean Systolic ± 2 S. D.	Mean Diastolic ± 2 S. D.
Newborn (*)	80±16	46±16
6 mo.-1 year (10)	89±29	60±10*
1 year (10)	96±30	66±25*
2 years (10)	99±25	64±25*
3 years (10)	100±25	67±23*
4 years (10)	99±20	65±20*
5- 6 years (9)	94±14	55± 9
6- 7 years (9)	100±15	56± 8
7- 8 years (9)	102±15	56± 8
8- 9 years (9)	105±16	57± 9
9-10 years (9)	107±16	57± 9
10-11 years (9)	111±17	58±10
11-12 years (9)	113±18	59±10
12-13 years (9)	115±19	59±10
13-14 years (9)	118±19	60±10

* In this study the point of muffling was taken as the diastolic pressure.
The number in parenthesis refer to the authors from whom the data were obtained.

TABLE 2.—*Recommended Cuff Width* *

Newborns	2.5 cm.
1 month-1 year	5 cm.
1 year-8 years	9 cm.
8 years+	12 cm.

General Rule: Cuff should cover two-thirds of the upper arm.

* References 7 and 8

Analysis of Case Material

Table 4 presents the pertinent findings in our nine patients. It may be seen that boys and girls are about equally represented. The age, at discovery of the hypertension, varied from 7/12 to 13½ years.

Five of the nine patients had headaches. Convulsions and hemiplegia, evidences of hypertensive encephalopathy, were present in two instances. Hemorrhages, occurring after minor surgery, led to discovery of the hypertension in two patients. Vomiting and weight loss were present in two youngsters. A positive family history of hypertension was elicited in five instances.

Physical examination revealed, in addition to the persistently elevated blood pressure, retinal changes in the five patients with the severest hypertension. Two of these were admitted with convulsions, followed by transient hemiparesis. One patient now is a deaf mute. The one fatal case in the series developed convulsions and coma preterminally. One patient had generalized neurofibromatosis. Otherwise the physical examinations were normal.

X-ray evidence of enlargement of the left ventricle and electrocardiographic signs of left ventricular hypertrophy were noted also in the five patients with severe hypertension. Electroencephalograms revealed nonspecific abnormalities, varying from diffuse slowing to widespread fast activity without focal discharges, in five patients. Pneumoencephalography was performed with normal results in four patients to exclude intracranial neoplasm. Exhaustive examinations of the urinary tract failed to reveal significant abnormalities in any patients.

Cold pressor tests were deemed feasible only in the six patients with a lesser degree of hypertension, and none responded with a systolic elevation of more than 25 mm. Only a borderline increase (20-30 mm.) in diastolic pressure was observed in four of the six patients tested—the other two showed no significant rise.

By contrast, only in the severe hypertensive patients was a sedation test worthwhile. Two of five had a significant drop in pressure.

Several tests for pheochromocytoma were performed in each of the nine patients. All were negative. Urinary catechol amine level, measured in one patient, was normal.

Surgical exploration for discovery of renal disease or pheochromocytoma was performed in the five severely ill patients. No significant abnormality was discovered. Aortograms were performed in two of the five patients with severe hypertension; both were normal.

TABLE 3.—*Causes of Hypertension in Infants and Children Diagnostic Aids*

Etiology	Diagnostic Aids
I. Renal	Clinical picture Repeated urinalyses, Addis count Concentration test, NPN Urea and creatinine clearances Renal biopsy
a. Acute and chronic glomerulonephritis Chronic nephritis secondary to anaphylactoid purpura	
b. Pyelonephritis	Repeated urinalyses Repeated urine cultures plus above tests in chronic cases
c. Polycystic renal disease	Intravenous Pyelogram Retrograde Pyelogram "Split" renal functions Exploratory laparotomy and renal biopsy
d. Tumors: Wilms and neuroblastoma	
e. Ectopic kidney	
f. Hypoplastic kidney	
g. Hydronephrosis	
h. Renal artery and vein anomalies and thromboses	Above tests plus aortogram and "Split" renal functions
i. Polyarteritis, disseminated lupus erythematosus	Clinical and laboratory signs of vascular disease plus renal biopsy
j. Primary arteriolar disease of the kidney	Azotemia, urine sediment abnormalties renal biopsy or necropsy
II. Central Nervous System	
a. Poliomyelitis	Clinical picture Lumbar puncture
b. Encephalitis	Above plus electroencephalogram
c. Brain tumor	Skull x-rays Above plus pneumoencephalogram or ventriculogram
III. Cardiovascular	
Coaretation of aorta	Femoral pulses (strength and timing compared with radial) Blood pressure in legs X-ray picture (collaterals and barium esophagogram)
Patent ductus arteriosus	Continuous murmur 2nd LICS ECG—left ventricular hypertrophy Cardiac fluoroscopy Rarely retrograde aortography
IV. Endocrine	
Secondary to cortisone or corticotropin (ACTH) therapy	History
Pheochromocytoma	History, IVP, Phentolamine (Regitine)-benzodioxane tests Histamine test Urinary or blood catechol amine test
Cushing's syndrome	Clinical picture Endocrine studies
Congenital adrenal hyperplasia	Clinical picture 17-ketosteroid excretion
V. Poisonings	
Lead	Clinical picture Anemia, stippled cells Spinal fluid (elevated pressure and protein) Glycosuria X-ray of long bones and skull Urine coproporphyrin (qualitative) Urine lead excretion (quantitative)
Mercury	Clinical picture of acrodynia Urine mercury excretion
VI. Essential	Positive family history ? cold pressor and amobarbital (Amytal) tests

Various other laboratory tests are included in Table 4. None revealed abnormalities.

The five patients (patients 1-5) with severe hypertension (160/110 mm. Hg or above) varied from 7/12 to 12 years of age at the time of discovery of their hypertension. All had symptoms attributable to their hypertension and all showed evidence of secondary vascular changes:

TABLE 4.—*Essential Hypertension—Children's Medical Center Cases*

Patient Number	1	2	3	4
Sex	Male	Female	Male	Male
Age				
At discovery of hypertension	11 9/12 yr.	7 4/12 yr.	6 10/12 yr.	7/12 yr.
At present	15 yr.	Died 10 yr.	16 yr.	9 yr.
Symptoms:				
Headache	+	+	+	+
Convulsion	0	+	0	0
Hemiplegia	0	+	0	0
Bleeding	+	0	+	0
Weight loss	0	0	+	+
Vomiting	0	0	0	+
Family History	0	0	0	0
B.P.: average	190/150	170/120	170/120	225/150
maximum	275/170	245/110	205/160	250/160
P.E.: Fundi	Gr. 2	Gr. 2	Gr. 1	Gr. 1
Femoral pulse	Normal	Normal	Normal	Normal
Neuro. exam	Normal	Normal	Normal	Deaf mute
Lab.: ECG	L.V.H.	L.V.H.	L.V.H.	R.A.D.
Chest X-ray	E.H.	E.H.	E.H.	E.H.
EEG	Abnormal	Abnormal	Normal	Normal
P.E.G.	Normal	Normal	Normal	
N.P.N.	27-31 mg. per 100 cc.	26-35 mg./100 cc.	34 mg./100 cc.	33 mg./100 cc.
Urine: Max. S.G.	1.033	1.027	1.034	1.020
Albumin	0	0	0	4+0
Microscopic	Negative	Negative	Negative	RBC, casts 4+0
Addis count	Negative		Negative	
Urea clearance	Normal			69% of normal
Creatinine Clear.	Normal			
I.V.P.	Normal	Normal	Normal	Normal
Cold Pressor			+25/30	
Sedation	No drop	−55/10	−28/30	
Benzodioxane	Negative	Negative		
Phentolamine	Negative	Negative	Negative	Negative
Histamine				
Exploration	Normal	Normal	Normal	Normal
Biopsy: Kidney		Normal	Minimal arteriolar sclerosis	Normal
Adrenal	Normal			Normal
Other Tests	Audiogram—Neg. Aortogram—Neg. PBI—normal Urine catechol amines—normal	Aortogram—Neg. PBI, 17-KS—normal Split renal funct.—normal GFR, RPF, FF—normal	Urinary corticoids—normal PSP—normal	17-KS—normal
Course	See Fig. 1 No progression of fundi, ECG, or x-ray Pt. also has neurofibromatosis Sympathectomy refused	See Fig. 2 Hemiplegia cleared in 3 weeks Died from a hypertensive crisis after medications were discontinued No post-mortem exam.	See Fig. 3 Pt. is asymptomatic, has normal growth, no progression of fundi, ECG, or x-ray.	Pt. had bilateral sympathectomy age 10 mo.; no reduction of B.P. which is now 205/130 Growth-normal No symptoms No progression of vascular complications

enlarged heart, left ventricular hypertrophy by electrocardiogram, and hypertensive retinopathy. One of the five succumbed with hypertensive encephalopathy, while the disease showed no significant progression in the other four during a follow-up period of 4 to 10 years. Only one of this group had a family history of hypertension.

The four remaining patients (6-9) had milder degrees of hypertension; pressures above 160/110 were never observed in these children. Their hypertension was discovered in late childhood—after age nine in every case. A strong family history of essential hypertension was elicited in all. This group was singularly symptom free. At the writing of this report, no secondary vascular changes, fatalities, or increase in severity of the hypertension have been observed during a follow-up period varying from 2 to 15 years.

Differential Diagnosis

Table 3 summarizes the most important etiological factors causing high blood pressure in children with appropriate diagnostic tests for their identification.

Renal disease is the most important cause of elevated blood pressure in children.[4] Hypertension presently explainable on the basis of renal disease may usually be identified by the following tests: repeated careful urinalyses, urine concentration tests, Addis counts, urine cultures, nonprotein nitrogen blood levels, intravenous pyelography, and simple renal function tests (urea and

TABLE 4.—*Essential Hypertension—Children's Medical Center Cases*—Continued

5	6	7	8	9
Female	Male	Female	Female	Male
4 ½ yr. 13 yr.	13 yr. 15 yr.	9 3/12 yr. 23 yr.	11 1/12 yr. 14 yr.	13 7/12 yr. 15 yr.
0	+	+	0	+
0	0	0	0	0
+	0	0	0	0
+	0	0	0	0
0	0	0	0	0
0	0	0	0	0
+	0	0	0	0
0	+	+	+	+
160/120	140/90	150/100	150/85	150/90
190/160	160/90	170/110	170/110	160/100
Gr. 2	Normal	Normal	Normal	Normal
Normal	Normal	Normal	Normal	Normal
Normal	Normal	Normal	Normal	Normal
L.V.H.	Normal	Normal	Normal	Slight L.V.H.
E.H.	Normal	Normal	Normal	Normal
Abnormal	Abnormal			Abnormal
Normal				
36 mg./100 cc.	40 mg./100 cc.	28 mg./100 cc.	35 mg./100 cc.	40 mg./100 cc.
1.019	1.020	1.024	1.030	1.018
0	0	0	0	0
Negative	Negative	Negative	Negative	Negative
Negative	Negative	Negative	Negative	Negative
Normal	Normal	Normal	Normal	Normal
	Normal		Normal	Normal
Normal	Normal	Normal	Normal	Normal
+8/2	+25/20	+12/20	0	+16/30
−10/4		−12/0		
Negative				
+15/5	+20/0	+2/2	+10/8	+8/0
Normal				
Normal				
Normal			PSP—normal	
Audiogram—Neg.			Skull x-ray—normal	
See Fig. 4 Pt. is asymptomatic with no progression of fundi, ECG, or x-ray.	After 11 mo. BP remained elevated Given reserpine (Serpasil) 1.5 mg. per day with reduction of BP to 122/80; he has no symptoms	BP has remained elevated at the same levels; At age 22 yr. she developed multiple sclerosis; No antihypertensive drugs have been given	BP remained elevated for 2 yr.; then given Alseroxylon (Rauwiloid) 10 mg. per day with reduction of BP to 126/80; she is asymptomatic	B.P. remained elevated for 6 mo.; Then on Alseroxylon (Rauwiloid) 12 mg. per day with no BP change; hydralazine (Apresoline) 200 mg. per day has also had no effect

Blank space ..... not recorded
L.V.H. ..... Left ventricular hypertrophy
E.H. ..... Enlarged heart
P.E.G. ..... Pneumoencephalogram
GFR ..... Glomerular filtration rate
RPF ..... Renal plasma flow
FF ..... Filtration fraction
R.A.D. ..... Right axis deviation

creatinine clearances). In patients with severe hypertension or hypertension known to be of recent origin, a special effort must be made to exclude unilateral renal disease. A wide variety of such unilateral lesions have now been reported to cause hypertension (pyelonephritis, anomalies or aneurisms of renal artery or vein, thromboses and infarcts, hydronephrosis, and ectopia of one kidney).‡ These may be diagnosed by intravenous and retrograde pyelography, differential ("split") renal function studies, aortography, and in some cases exploratory laparotomy with careful palpation of the renal vessels and biopsy of the kidneys. Although cure of the hypertension does not invariably follow unilateral nephrectomy in these cases,[13] the occasional dramatic results and the hopeless prognosis without therapy justify removal of the affected kidney.

History of a preceding disease such as acute glomerulonephritis or nephrotic syndrome is also suggestive of the renal origin of the hypertension. Although usually such cases will show definitely abnormal urinary sediment or abnormalities of renal function, we have seen

‡ References 12-15.

one patient with hypertension in whom a clear-cut episode of periorbital edema and gross hematuria was followed by a period when urinary sediment and renal functions were normal, yet persistent hypertension was present. This is similar to the case described by Fomon, Kaplan, and Brodsky.[16]

The attempt to separate essential from renal hypertension is made more difficult by the secondary renal changes caused by long-standing hypertension. Nevertheless, in the present state of knowledge the renal origin of hypertension may be established if pertinent history or laboratory data are abnormal—in their absence other entities must be considered.

Central nervous system diseases such as acute or chronic poliomyelitis,[17] encephalitis, and brain tumor can usually be diagnosed by the clinical picture, cerebrospinal fluid findings, skull x-rays, electroencephalogram, and occasionally air-injection studies. The syndrome of familial dysautonomia (Riley-Day)[18] can usually be recognized by the labile hypertension with marked postural changes, absence of tearing, hypesthesia, repeated febrile episodes, frequent respiratory infections, motor disturbances, and mental retardation.

Cardiovascular diseases are most readily identified by the physical examination. The determination of blood pressure in the legs as well as in the arms will reveal the presence of a coarctation of the aorta. Auscultation of the heart should rule out patent ductus arteriosus and aortic insufficiency. Arteriovenous anastomosis, in common with patent ductus arteriosus and aortic insufficiency, produce a wide pulse pressure and the additional finding of a continuous murmur over the lesion.

The most frequent endocrine cause of hypertension today is prolonged administration of corticotropin (ACTH) or cortisone.[19] The clue to this diagnosis is obviously a careful history.

The diagnosis of pheochromocytoma is more difficult. This tumor is rare in children; only 16 authenticated cases have been reported.[20] The classical clinical picture of paroxysmal hypertension with signs of increased circulating epinephrine or norepinephrine is not found in all cases. Since these tumors may mimic any type of hypertension, screening tests to determine their presence must be performed on all patients with hypertension. These tests are the phentolamine (Regitine) hydrochloride adrenergic blocking[21] and histamine provocative tests.[22] The former is indicated in cases with elevated blood pressure at the time of the tests (above 160/110), whereas the intravenous histamine test is recommended if no significant hypertension is present at the time of testing. This provocative test may be dangerous by provoking a hypertensive crisis and phentolamine hydrochloride should be at hand to block such an event.

In cases with positive tests intravenous or retrograde pyelography may reveal the site of the tumor. Twelve per cent of pheochromocytomas lie outside the adrenal area,[23] however, and are not demonstrable by any x-ray studies. Exploratory laparotomy with search along the entire sympathetic chain is indicated in any suspicious case and at times exploration of the chest may be necessary.

The recent development of a test for increased urinary catechol amines[24] has provided a safe and probably reliable diagnostic procedure, but one which is available in only a few medical centers. By using the easily available tests as described and surgically exploring the suspicious cases, this tumor can usually be excluded with confidence.

Hyperthyroidism, Cushing's syndrome, and acromegaly may be diagnosed by the usual clinical and laboratory methods.

Poisonings that produce hypertension can usually be excluded by history. The diagnosis of chronic lead poisoning may be made by the usual clinical and labora-

tory findings. Qualitative urinary coproporphyrin and quantitative 24-hour urinary lead excretion tests have helped greatly in the diagnosis of this poisoning.[25] Mercury intoxication is rare today but should be considered when signs and symptoms of acrodynia occur.[26]

Essential hypertension, then, is principally a diagnosis to be considered by excluding the foregoing disease groups. Since many of the other diseases (unilateral renal disease and coarctation especially) are curable, every effort should be made to exclude these before the diagnosis of essential hypertension is made.

It has been claimed that the cold pressor test is consistently positive in cases of essential hypertension, but a recent study[27] has cast doubt on the validity of this assumption. It is a useful diagnostic test, however, for those patients who do not have an extreme fixed degree of hypertension. A positive family history is to date the most helpful finding in the diagnosis of essential hypertension—a fact recognized for many years.[28]

Transient systolic hypertension is observed relatively commonly, particularly in adolescents. Graham, Hines, and Gage[9] found a systolic hypertension of 135 mm. Hg or above in 305 of 21,026 blood-pressure determinations in children 14 years and under. In only 3 of 19,771 determinations was a diastolic pressure over 90 mm. Hg found (Table 5). These were but single recordings and, although the children were presumably normal, no laboratory studies were made to rule out diseases such as chronic nephritis, since these children were examined when under basal conditions the figures indicate only the minimum frequency with which single systolic readings in the hypertensive range may be observed in childhood.

Whether transient elevations of both systolic and diastolic readings should be considered a precursor of essential hypertension is a widely debated question. Hines[29] studied 1522 adults 10-20 years after initial blood pressure determinations. Of those with initial readings under 140/85 mm. Hg only 3.8% had hypertension 20 years later, whereas of those with transient elevations above 140/85 mm. Hg on the initial visit, 82.5% had a persistent hypertension when studied 20 years later. Levy and coworkers,[30] in a survey of army officers,

TABLE 5.—*Incidence of Hypertensive Blood Pressures in Presumably Normal Children*
Total Number of Children, 3580 *

Age	Number of Blood Pressure Determinations				
	Systolic (Mm. Hg.)			Diastolic (Mm. Hg.)	
	Total No.	135-159	160+	Total No.	90+ (none above 99)
5 yr.	1470	1	0	1149	0
6 yr.	1684	0	0	1278	0
7 yr.	1911	0	0	1498	0
8 yr.	2076	5	0	1614	0
9 yr.	2176	3	0	1724	0
10 yr.	2320	14	0	1839	0
11 yr.	2335	34	3	1928	0
12 yr.	2575	59	1	2043	3
13 yr.	2363	78	3	1987	0
14 yr.	2096	98	6	1878	0
15 yr.	1657	113	9	1568	0
16 yr.	1259	105	6	1245	0

* Many children had readings yearly.
(Adapted from Graham, Hines, and Gage [9])

found sustained hypertension 2.8 to 4.8 times more frequently in those who, five or more years previously, had shown transient hypertension than in those who had not.

As Sobel[31] and others have emphasized, it may be from this group of children with labile hypertension, during the stress of a physical examination, that the majority of adults with essential hypertension will be recruited.

Review of Literature

Sobel[31] in 1941 reported that there were "less than 100" cases of essential hypertension in children in the world literature. Only a few single case reports have been presented since. Most of the patients reported could not be labelled as having essential hypertension by today's standards. In some instances information which we now regard as indispensable for the establishment of this diagnosis was not available (pyelography, renal function studies, and tests for pheochromocytoma). In other cases evidence of conditions which we now know can cause hypertension—atrophic kidney, cerebral tumors, and chronic renal disease—was presented but not correctly interpreted because these conditions were not at that time recognized as causes of hypertension.

An evaluation of the English literature using present-day criteria reveals only 10 cases of well-substantiated essential hypertension in children 14 years of age and under.§ The age of these patients ranged from $1\frac{11}{12}$ to 13 years; four were boys and six were girls. The hypertension was of a severe degree in most instances. Symptoms and signs of vascular damage were commoner in the group with a blood pressure of 160/110 or over. Family history was negative for essential hypertension in 8 of the 10 cases where this information was recorded.

§ References 31-36.

Many other cases reported as having essential hypertension‖ were diagnosed clinically as having malignant hypertension. At postmortem examination these had chronic renal lesions in which chronic glomerulonephritis, polyarteritis, or pyelonephritis were the probable causes of the hypertension.

Therapy

Our experience in the treatment of children with essential hypertension is much too limited for any definite conclusions. A vast amount of experience, however, has been recorded in adults.¶ From these exhaustive reports and our limited experience, we have formulated our present therapeutic approach.

Mild sedation with phenobarbital, weight reduction for the obese, and superficial psychotherapy have been the mainstays of treatment for essential hypertension for many years and have played an important role in the management of our patients. Restriction of physical activity has been frequently advised for the therapy of hypertension in the past. We have found no conclusive evidence that this in fact benefits these patients—on the contrary, if it increases anxiety and tension it may lead to further elevation of the blood pressure. Therefore we have allowed our patients full physical activity with two exceptions: (1) that they cease exercise if symptoms occur—headaches, palpitation, chest pain, or dyspnea—and (2) competitive interscholastic athletics are discouraged.

Low-sodium diet has been effective in adults but must be extremely rigid to be of value. This diet has not been practical in children because of their refusal to take such a diet and the failure of this small amount of sodium to allow for growth. Adrenalectomy has seemed to present too many problems in management to be attempted. Formal psychiatric evaluation

‖ References 37-42.

¶ References 43-48.

has been carried out in three patients. In two the indications were overt behavior problems rather than the hypertension. In the third patient psychotherapy was not felt to be indicated after psychiatric studies had been completed.

Antihypertensive drug therapy and sympathectomy are generally agreed to be the major treatments of benefit today. It seems wise to treat all patients with persistent hypertension with one or more of the modern drugs in an effort to lower the blood pressure and prevent progression of the disease to the malignant stage. It is recognized that many people have severe arterial hypertension for many years without complications but at present we are unable to separate them from the malignant group early enough. In some cases it will also be evident to the physician that the psychic problems induced by concern over taking medications may outweigh their potential value.

Table 6 outlines the various drugs available at present for the treatment of arterial hypertension in children, the mechanism of action, dosage, toxicity, and indications for each.

Our patients with mild hypertension (blood pressure under 160/110) have been started on rauwolfia serpentina in the doses indicated.# Every two-three weeks this dose was increased by one tablet per day until side-effects—drowsiness, nasal stuffiness, or diarrhea—became prominent. The dose was then decreased by one-two tablets to alleviate the toxic symptoms and the medication continued indefinitely.

At first we added veratrum preparations* orally to the rauwolfia but found no increase in the hypotensive effect, and usually disturbing symptoms of anorexia, nausea, and vomiting occurred. Hydralazine (Apresoline) hydrochloride† was added after several weeks of rauwolfia therapy if no significant reduction in blood pressure had been achieved. The dose was increased gradually to a maximum of 300-400 mg. per day. After prolonged high dosage, toxicity symptoms resembling disseminated lupus erythematosus and rheumatoid arthritis have been reported.[49] Though in all cases so far reported these symptoms have been reversible upon discontinuing the drug, we have been reluctant to use this agent for patients with only moderate hypertension because of this potential danger.

In the group of patients with severe hypertension (blood pressure over 160/110) one of the ganglionic blocking agents‡ has been added to the rauwolfia or rauwolfia plus hydralazine if these were not effective. Rauwolfia is particularly useful in combination with hexamethonium, since it counteracts to some degree the distressing side-effect of constipation seen in most patients taking hexamethonium. When administering the ganglionic blocking agents it is important to start with small doses and work up gradually to a dose producing hypotension or toxicity. Warnings must be given to these patients concerning constipation, urinary retention, and postural hypotension. Cathartics are prescribed to be taken at the first sign of constipation, and dosage is reduced if other symptoms appear. It is most important not to discontinue this drug suddenly as rebound hypertensive crisis may ensue.

For the group with the severest hypertension, sympathectomy is probably indicated if drug therapy is not effective. As noted by Reyersbach and Butler,[35] variable results have been obtained. On the basis of our limited experience it seems impossible to predict which pa-

Alseroxylon (Rauwiloid) was supplied by Riker Laboratories, Inc.; reserpine (Serpasil) was supplied by Ciba Pharmaceutical Products, Inc.

* Alkavervir (Veriloid) was supplied by Riker Laboratories, Inc.

† Hydralazine (Apresoline) hydrochloride was supplied by Ciba Pharmaceutical Products, Inc.

‡ Hexamethonium was supplied by Ciba Pharmaceutical Products, Inc.

TABLE 6.—*Therapy of Hypertension*

Drug	Site of Action	Initial Dose
Phenobarbital	Central	8-15 mg. q.i.d.
Rauwolfia serpentina	Central	Alseroxylon (Rauwiloid) [1] 1 mg. t.i.d. Serpasil [2] 0.1-0.25 mg. t.i.d.
Hydralazine (Apresoline) [3]	Central Mild ganglionic block	P.O. 10-20 mg. q.i.d. I.M. 0.2-0.25 mg./kg. q 4-6 hr.
Veratrum alkaloids	Reflex vasodilatation	
Protoveratrine		I.V. 1.5-1.9 mcg/kg. over 2 minutes —repeat q 3 hr.
Alkavervir (Veriloid) [2]		P.O. 3 mg. t.i.d.
Hexamethonium	Ganglionic block	P.O. 37.5-75 mg. q.i.d. I.V. 0.1-1.0 mg/kg. S.C. 0.1-1.0 mg/kg.
Trimethaphan camphorsulfonate (Arfonad)	Ganglionic block	I.V. 1 mg/cc. solution—start at about 60 drops/min.
Magnesium sulfate	Vasodilator	150-200 mg/kg. (5-7 cc. of a 3% sol.) I.V. in 1 hr. Titrate rate of infusion by B.P. Constant attendance mandatory

(1) Riker Laboratories, Inc., trade name
(2) Ciba Pharmaceutical Products, Inc., trade name
(3) Riker Laboratories, Inc., trade name

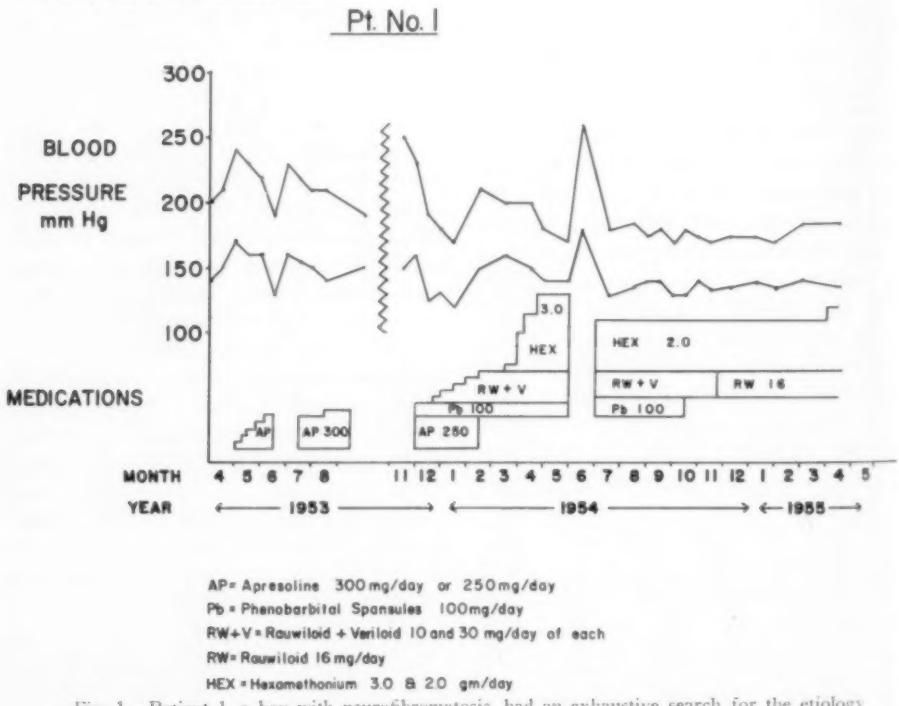

Fig. 1.—Patient 1, a boy with neurofibromatosis, had an exhaustive search for the etiology of his hypertension. None was found and he has been treated exclusively with varying medications because of parental refusal to permit a sympathectomy. It is interesting to note the rapid and marked rise in arterial pressure when all such drugs were discontinued in 1954 and the subsequent partial control with very large doses. In spite of very high blood pressure he is symptom free.

TABLE 6.—*Therapy of Hypertension*—Continued

Maintenance	Side-Effects	Indications
Increase to tolerance	Drowsiness	Mild case where anxiety is dominant
Increase to tolerance maximum 10-15 mg/day (1-2 mg. of reserpine)	Bradycardia, laxative, nasal congestion, sedation	Mild early cases, conjunction with other drugs
Increase to tolerance maximum 600-800 mg/day	L.E.—rheumatoid arthritis syndrome, headache, dizziness, hypotension, nausea, vomiting	Moderately severe cases
When hypotensive effect noted use 2½ –3X I.V. dose q 8-12 hr. S.Q. Increase gradually to tolerance	Nausea, vomiting, bradycardia, salivation, hypotension Antidotes atropine ephedrine	Parenterally in hypertensive crises Combined with other drugs may be useful P.O. in moderately severe cases
Increase to tolerance parenteral adm. q 6-12 hr. P.O. q.i.d.; continue I.V. drip at a rate necessary to maintain reduction of B.P.	Postural hypotension constipation, urinary retention, dry mouth	Severe cases Especially useful with other drugs Hypertensive Encephalopathy
When hypotensive effect use 0.2-0.4 cc/kg. of 25% sol. I.M. q 4 hr.	Central depression Respiratory and cardiac arrest N.B. Calcium gluconate should be at hand	For severe hypertensive crises—especially in renal disease

TABLE 6*A*.—*Other Forms of Therapy*

1. Low Sodium diet—too difficult to administer in children
2. Thoracolumbar sympathectomy—irregularly effective—severe progressive cases should receive
3. Adrenalectomy—too hazardous at present
4. Psychotherapy—Informal type plays role in treatment of all cases; formal type not evaluated as yet

tients will benefit from this procedure. Sedation tests have not been of value in selecting those candidates likely to be helped. Four of our patients with severe hypertension have had sympathectomies—two were benefitted and two were not.

In one, who had a striking fall of blood pressure following sympathectomy, there was no reduction with sedation (Case 5), while in another (Case 2), who obtained no relief from operation, there had been a good decrease in pressure with amobarbital sodium (Sodium Amytal)-induced sleep. One patient (Case 3), who had a moderate fall in blood pressure with sedation, also had a moderate fall after sympathectomy while the other patient to have such an operation did not have a sedation test performed preoperatively.

Figures 1 through 4 illustrate the clinical course as related to therapy of four of our patients with extreme degrees of hypertension. Three of our four patients with mild degrees of hypertension were treated with rauwolfia or its derivatives—two showed a reduction to normal levels while on therapy. The other patient has as yet not responded to the combination of rauwolfia and hydralazine.

Thus, in our small series, no uniform benefit with any one therapeutic regimen was obtained. This emphasizes the need for individualizing the therapy for each patient and the limitations of medical management at present.

Hypertensive encephalopathy occurred in two patients of this group. Whether secondary to essential hypertension or other causes, this complication represents

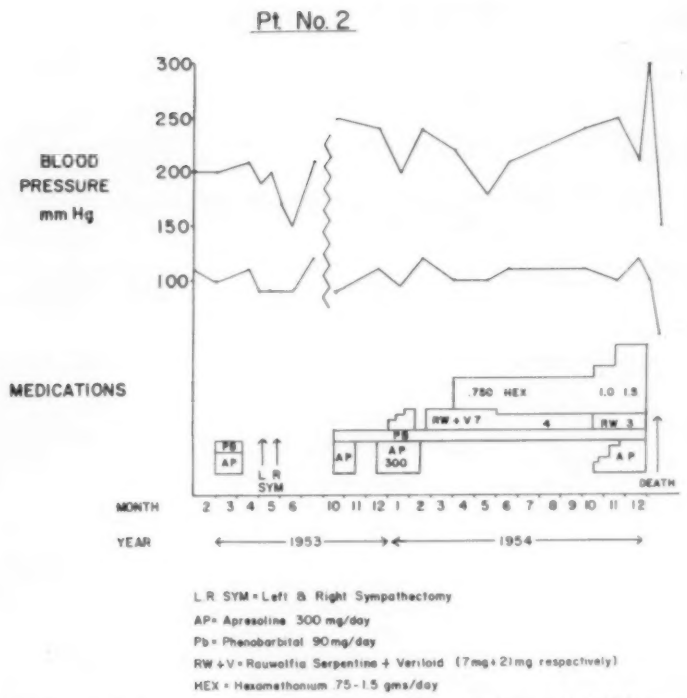

Fig. 2.—Patient 2, a girl, who was 10 years old when she died, had failed to respond to any therapy. It is important to note that when all medications were suddenly discontinued because of ileus, she developed hypertensive encephalopathy and died.

a medical emergency requiring intravenous hypotensive therapy. Although we have in the past used protoveratrine or hexamethonium with success, we have been most impressed recently by the ease and success with trimethaphan camphorsulfonate (Arfonad) used as outlined in Table 6.

Summary

Nine patients under 14 years of age with essential hypertension are presented. These were the only patients found in our hospital in a 15-year period who met the criteria for this diagnosis.

Secondary changes, in terms of cardiovascular and central nervous system complications, were noted only in the children with severe hypertension. One patient with severe hypertension died with hypertensive encephalopathy when medication was suddenly discontinued. The other 8 have shown no progression of their disease during a follow-up of 2 to 15 years.

The patients with milder elevations of blood pressure all gave a positive family history of hypertension, whereas but one of five patients with severe hypertension did.

The range of blood pressure in normal infants and children as reported in the literature has been tabulated.

The literature indicates that transient elevation of blood pressure in children may be the precursor of adult essential hypertension.

The differential diagnosis of hypertension in children is outlined. Essential hypertension is a rare disease in childhood and should be considered only after all other causes—especially renal—have been most carefully excluded.

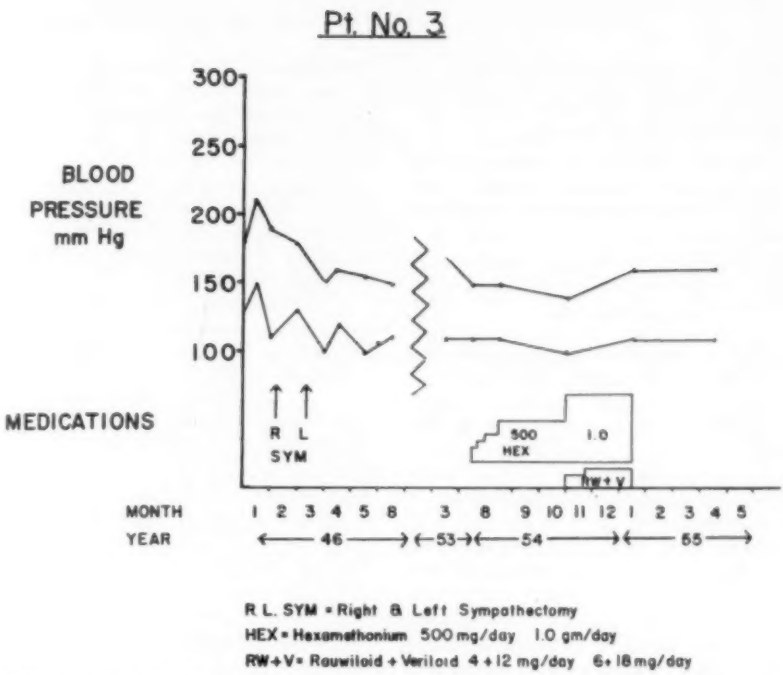

Fig. 3.—Patient 3, a boy, had a very good response to sympathectomy nearly 10 years ago. He did not respond with further reduction in blood pressure, however, when antihypertensive drugs were tried.

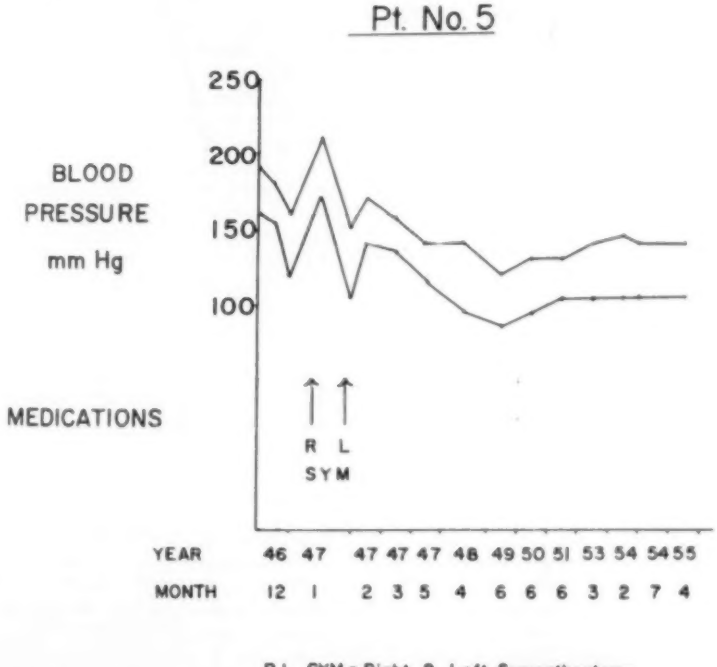

Fig. 4.—Patient 5, a girl, had a very marked and prolonged reduction of blood pressure following sympathectomy nine years ago.

Therapy of hypertension with antihypertensive drugs, sympathectomy, and other measures are reviewed.

Dr. L. Bruce Anderson and members of the House Staff of The Children's Medical Center assisted in the clinical management of many of these cases.

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Group A Beta Hemolytic Streptococci in Relation to Rheumatic Fever

Study of School Children in Miami, Fla.

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Because of the etiological relationship attributed to group A beta hemolytic streptococci in rheumatic fever, the pattern of infection with these organisms is presented for greater Miami (Dade County), Fla., an area where rheumatic fever is uncommon. In school children 6 to 9 years of age 25% to 40% of those studied by monthly throat swabbings have group A organisms in their throats at least once each 8-month school year. Groups and types of streptococci isolated are the same as in the North. Approximately 50% of children with such organisms show definite antistreptolysin O rises. Children from whom group A beta hemolytic streptococci (typable or nontypable) are recovered have higher average antistreptolysin O titers and indices than do those children from whom no beta hemolytic streptococci, or only groups of streptococci other than group A, are isolated.

The postulate that 3% of group A beta hemolytic streptococcal infections proceed to rheumatic fever if inadequately treated requires refinement of the concept of what constitutes streptococcal "infection." Our suggested criteria define overt, occult, and possible infection, anamnestic antibody response, and convalescent and healthy carrier state.

Possible climatic influences on the occurrence of rheumatic fever are discussed.

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From the Department of Medical Research, National Children's Cardiac Hospital, and the Department of Microbiology and the School of Medicine, University of Miami.

Five years ago, we reported [1] that rheumatic heart disease was uncommon in native-born children attending schools in southern Florida (Table 1). Our rate of 3 to 5 per 1000 was low when compared with the findings of similar studies carried out by cardiologists elsewhere in the United States. These observations * have been set on a contour map of the East Coast of the United States (Fig. 1). This figure demonstrates clearly the close parallel between prevalence rates of rheumatic heart disease and latitude, ranging from 3 cases per 1000 population at 25° N. latitude to 45 per 1000 at 45° N.

Since rheumatic fever is generally accepted as etiologically dependent on group A beta hemolytic streptococci, and since it has been stated that this relationship is quantitative, with "relatively little direct effect of altitude, climate, or humidity on the attack rate of rheumatic fever," [9] it was logical to investigate the streptococcal pattern in this far southern area, first, as to frequency, and then as to responses observed in the subjects studied.

The low rheumatic fever rate in Miami might be attributed to one or more of several possibilities:

* References 1-8.

1. Streptococci were relatively uncommon in the South.

2. Streptococcal groups, types, and strains varied from those found elsewhere.

3. Streptococci were so altered in antigenicity or virulence that they did not produce the same antibody responses in the host as in more northerly areas.

4. Host susceptibility to rheumatic fever was decreased in the South.

5. Additional factors were implicated in the pathogenesis of rheumatic fever.

TABLE 1.—*Rheumatic Heart Disease in Miami-Born School Children (1950)*[1]

	Number Examined	R.H.D., Definite	R.H.D., Suspected	Total
White	579	0	0	0
Negro	422	3	2	5
Total	1001	3	2	5

Our studies in Miami school children from February, 1953,[10] through May, 1955, were designed to furnish data regarding the first three possibilities.

Methods and Results

A total of 6400 throat cultures were taken monthly during the school year from 740 children attending the first three grades in three of the Miami public schools (Tables 2 and 3). Each culture was taken by swabbing the throat simultaneously with a pair of sterile cotton swabs held together by the technician. Laboratory isolation of beta hemolytic streptococci was carried out as previously described.[10] Whenever such organisms were recovered, they were sent to the Streptococcus Laboratory of the United States Public Health Service, Communicable Disease Center, for grouping and typing under the supervision of Dr. Elaine L. Updyke.

As can be seen from Table 4, 25% to 40% of the children harbored group A beta hemolytic streptococci in their throats at least once during

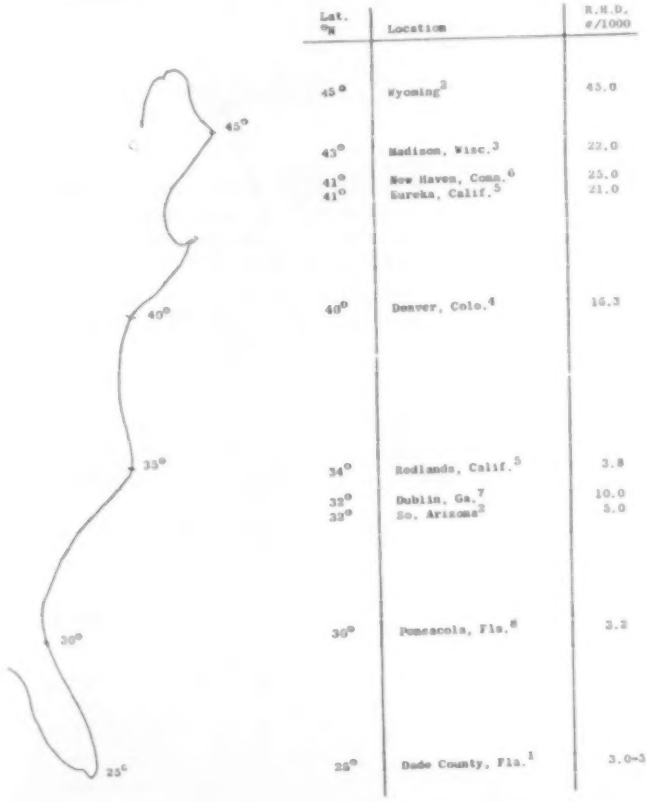

Fig. 1.—Effect of latitude on the number of cases of rheumatic heart disease reported per 1000 children in various localities.

TABLE 2.—*Number of Pairs of Throat Cultures Taken from Miami School Children (1953-1955)*

Year of Study	Total Cultures (3 Schools)	Special Study (48 Schools)	Total Cultures
1953 (4 mo.)	1154	...	1154
1953-1954 (8 mo.)	2809	...	2809
1954-1955 (8 mo.)	2437	1200	3637
Total	6400	1200	7600

TABLE 3.—*Number of Children Studied*

	1953 (4 Mo.)	1953-54 (8 Mo.)	1954-55 (8 Mo.)	Total
Total No. participants	343	417	333	1093
No. carried over from 1st year	0	186	82	...
No. carried over from 2d year	0	0	85	...
No. children new to study	343	231	166	740

any one eight-month school year. Several children carried more than one type at different times.

To determine the applicability of these findings to other school children of the same age, a concurrent special study was carried out between October, 1954, and May, 1955, in 1200 additional children attending 1 of 48 other schools (25 children in each school) in Dade County (Table 2). A paired throat culture was taken only once from each child.

The maximal and minimal, as well as the average, monthly isolation rates are shown in Table 5 for each month of each year's study and for the special study. The over-all monthly figure was 11.2%.

Grouping and typing of the beta hemolytic streptococcal strains (Table 6) failed to reveal any significant difference in the groups and types of streptococci isolated in Miami, as compared with those reported elsewhere. In addition to the types tabulated, several cultures listed as nontypable were subsequently shown to be the new type Red Lake.† Those strains reported as nontypable are recorded in Table 7. It was obvious from our studies that group A beta hemolytic streptococci can be recovered commonly from the throats of Miami school children.

† References 11-13.

TABLE 4.—*Number and Per Cent of Children Positive for Group A Beta Hemolytic Streptococcus One or More Times During Study*

Year	No. Children Studied	Children Positive at Least Once		Individual ABHS* Infections No.
		No.	%	
1953 (4 mo.)	343	46	13.4	47
1953-1954 (8 mo.)	417	126	30.2	133
1954-1955 (8 mo.)	333	135	40.4	150

ABHS = Group A beta hemolytic Streptococcus.

TABLE 5.—*Monthly Isolation Rate of Group A Beta Hemolytic Streptococci*

	1953 %	1953-54 %	1954-55 %	Special Study (1954-55) %
Oct.	...	6.3	10.2	5.3
Nov.	...	9.1	13.3	16.7
Dec.	...	3.8	12.0	...
Jan.	...	6.9	12.5	13.3
Feb.	2.5	10.6	16.8	17.3
March	3.6	7.4	16.9	20.0
April	5.7	10.4	15.3	14.0
May	8.7	10.5	17.1	9.3
June	...	...	...	18.0
Average	5.1	8.1	14.2	14.25

TABLE 6.—*Group A Typable Beta Hemolytic Streptococci Recovered*

Types	1953 (4 Mo.)		1953-54 (8 Mo.)		1954-55 (8 Mo.)		Special Study (8 Mo.)	
	No. Strs.	No. Child.	No. Strs.	No. Child.	No. Strs.	No. Child.	No. Strs.	No. Child.
1			17	10*	7	3‖	17	17
3			5	1			2	2
4			13	10	37	17†	11	11
5							1	1
6					54	23‡	3	3
8							2	2
11					1	1		
12	26	23	26	14*	12	3‡	17	17
13					3	1		
23			1	1				
28	1	1	3	3			1	1
31			2	2				
33			2	2	8	3†	1	1
36							1	1
39					2	2		
43					1	1		
44			1	1	3	2	1	1
Total	27	24	72	44	128	56	57	57

* Denotes one child with two different typable organisms at different times; child listed in A 12 (Group A, type 12) column only.
† = A 1, A 6, and A 33 at different times, listed in A 1 (one child).
‡ = Two with A 1 and A 12, listed in A 6.
‖ = One with A 1 and A 6, listed in A 6.

The next step was the determination of antistreptolysin O titers in order to see whether production of this antibody, one systemic response to streptococcal infection, had been evoked in the children studied. For this purpose, approximately 1400 blood samples were drawn during the latter two years of the study, at the same times that throats were swabbed. From 1953 to 1954, blood was taken from each child every other month. In the subsequent study year, blood samples were drawn from each subject in October, 1954, and in May, 1955; whenever beta hemolytic streptococci were recovered from any child, additional blood was collected 2, 4, 8, 16, and 32 weeks later during the school year. B-D Vacutainers,† the use of which greatly curtailed hemolysis, were employed. Levels of antistreptolysin O in the sera were titrated by the technique recommended by Difco Laboratories, using Difco streptolysin O reagent.

In addition to calculating an average antistreptolysin O titer, we also developed an antistreptolysin O index[14] for each bacteriological category and for each year. The method for calculation of anistreptolysin O index is as follows:

$$\text{ASLO Index} = \frac{(R_1 \times S_1) + (R_2 \times S_2) + \ldots + (R_n \times S_n)}{\text{Total Samples per Bacteriologic Category}}$$

Where

R = arithmetic rank of progressive ASLO titers (1= titer of < 12; 2=12; 3=50; 4=100; 5=125; 6=166; 7=250; 8=333; 9=500; 10=625; 11=833; 12=1250).

†Supplied by Becton-Dickinson & Co., Rutherford, N. J.

TABLE 7.—*Group A Nontypable Beta Hemolytic Streptococci Recovered*

	Total No. Children	Total No. Cultures	No. Children Positive	No. Strains Recovered	No. Strains per Child
1953 (4 mo.)	343	1,154	22	32	1.5
1953-54 (8 mo.)	417	2,809	90	152	1.7
1954-55 (8 mo.)	333	2,437	99	227	2.3
Special Study (8 mo.)	1,200	1,200	114	114	....

TABLE 8.—*Average Antistreptolysin O Titers and Indices*

Bacteriological Category	1953-1954		1954-1955	
	Titer	Index	Titer	Index
No beta Strep. or group B only	81	3.5	66.1	3.1
Group C, F, or G.	119	4.6	116.4	4.4
Group A, nontypable	134	4.6	140.8	4.6
Group A, typable	120	4.4	142.9	5.0
Average	100	4.0	102.8	4.0
Total Sera	996		468	

S = No. of samples in the corresponding rank. This index has the advantage of obviating the skewing of averages which commonly results from a relatively small number of samples with very high titers. Table 8 is a compilation of titers and indices for the two years reported. The 996 sera from 1953 to 1954 constitute all the samples collected that year. The 468 sera described for 1954-1955 represent all 234 children from whom both initial and final blood samples were available. Table 8 indicates that the children from whom group A streptococci were isolated had higher average antistreptolysin O titers and indices than those from whom no beta hemolytic streptococci were recovered.

Group B streptococci do not produce streptolysin O,[15] and those children from whom these organisms were isolated were classified with those children from whom no streptococci were recovered. Groups C and G organisms may produce streptolysin O,[16] for which reason they were listed together. Titers associated with group A organisms were appreciably higher than those with streptococci of other groups.

Significant antistreptolysin O responses, as judged by a two-tube or greater rise, occurred in 50.7% of the children from whom group A beta hemolytic streptococci had been recovered, as contrasted with only 8.6% of the children who did not yield group A streptococci (Table 9). These data are available only for the second year of the blood studies, because appropriately timed follow-up blood samples after recovery of streptococci were collected only during 1954-1955.

TABLE 9.—*Significant Antistreptolysin O Titer Rises (1954-1955)*

Bacteriological Category	No. Children	No. with <2-Tube Rise	No. with Two-tube Rise or >	
			No.	%
No beta hem. Strep. or group B only	101	96	5	5.0
Group C, F, or G.	39	32	7	17.9
Total non-group A	140	128	12	8.6
Group A, nontypable	43	23	20	46.5
Group A, typable	24	10	14	58.3
Total group A	67	33	34	50.7

Comment

Our studies demonstrate the following:

1. Group A beta hemolytic streptococci are common in Miami children, 6 to 9 years of age.

2. Groups and types are the same as elsewhere.

3. Group A beta hemolytic streptococcal strains isolated do evoke at least one systemic response (as judged from antistreptolysin O titrations) in 50% of the children in Miami from whom these organisms were recovered.

What then do our findings mean in terms of "infection"? If every Streptococcus recovered signifies an infection, then of the 35,350 children enrolled in the first three grades of the Dade County public schools (Table 10), 40% or 14,140 children who probably harbored streptococci in their throats some time during the eight-month period of our study (1954-1955), may be considered to have had infections. If we consider as infections only these children, 50%, with significant antistreptolysin O rises, then the number of children with infection drops to 7070.

On the basis of the postulate that 3% of untreated streptococcal infections result in acute rheumatic episodes,[9] 212 attacks of

TABLE 10.—*Data Obtained in Study Projected to Total Dade County School Population (1954-1955)*

Actual No. of children enrolled in 1st 3 grades	35,350
Projected No. positive for Group A beta hemolytic streptococci at least once in 6 months (40%)	14,140
Projected No. with significant antistreptolysin O rise (50%)	7,070
Projected No. of expected attacks of rheumatic fever (3%)	212
Actual No. of cases of active rheumatic fever reported, entire State of Florida in 14 months ending March 1, 1956	73

acute rheumatic fever would be anticipated in just the 6-to-9-year age group for the study year. This was not so. None of the children in our study developed rheumatic fever. A rheumatic fever and rheumatic heart disease case register, which is being maintained for the entire state of Florida under the supervision of Dr. S. D. Doff, Director of the Division of Heart Disease Control, Florida State Board of Health, the Florida Heart Association, and the National Children's Cardiac Hospital, revealed a total of only 73 reported cases of active rheumatic fever during 14 months ending March 1, 1956. The case register includes all children up to 18 years of age, and serves to show the small number of cases on record in Florida.

How can the discrepancy between the large number of streptococcal isolates and the low incidence of rheumatic fever in Miami be explained? The discrepancy may lie either in the definition of what constitutes a streptococcal infection or in the inapplicability of the 3% rate in a tropical climate, or in some combination of the two.

In considering the term "streptococcal infection," there is ambiguity in the literature as to what constitutes "infection." It seemed to us that a helpful classification could be established, based on clinical, bacteriological, and immunological findings. Table 11 presents our suggested guide for determining streptococcal status.

In view of these proposed definitions, the quantitative estimate of 3% of streptococcal infections resulting in rheumatic fever does not apply in southeast Florida to any but the overt infections, if at all.

It is our concept that there is a balance between the "rheumatogenicity" of the bacteria and/or their toxic products and the host's resistance. This interrelationship between infection with group A beta hemolytic Streptococcus and subsequent development of rheumatic fever depends on factors in addition to the mere presence of the organisms. A concomitant virus also may be involved.[16]

Host defenses against streptococci may be maintained at a high level in Miami by climatic and other environmental factors. According to Köppen and other geographers [17] the southeast coast of Florida is the only area in the United States with a "tropical" climate, that is, a locality where the

TABLE 11.—*Suggested Criteria for Evaluation of Streptococcal Status*

Evidence		Clinical	Bacteriological	Immunological
I. Overt infection		+	+	+
II. Occult infection or convalescent carrier		−	+	+
III. Possible infection	A.	+	−	+
	B.	+	+	−
IV. Healthy carrier		−	+	−
V. Anamnestic response	A.	−	−	+
	B.	+	−	+

average temperature of the coldest month is above 64.4 F. Miami lies at 25° 47′ N. latitude—the southernmost large city in the United States. As such, it receives more solar radiation in the wintertime than any other city; first, because in the winter the obliquity of the sun's rays is least, and, second, because the days are longest. With increased insolation, there is correspondingly more ultraviolet radiation.

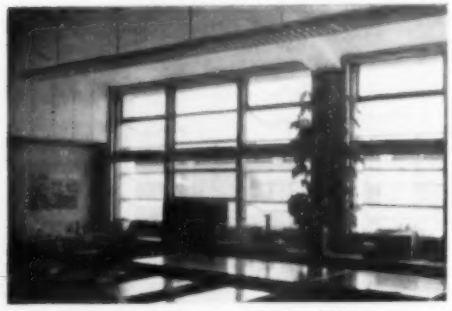

Fig. 2.—Schoolroom, Miami, Fla.

Children attending our local schools (Fig. 2) are exposed indoors to more ventilation, and outdoors to more ultraviolet per unit of time and for longer periods of time during the winter months than is possible in the North. The opportunity for cross-spraying due to overcrowding and climatically enforced indoor living is reduced. In this manner perhaps the number of different types of group A streptococci that a child encounters per unit of time is greater in northern than in southern localities. These and other factors probably exert their influence on the frequency of rheumatic fever. The development of this disease cannot be attributed to the mere presence of group A beta hemolytic streptococci, which appear to be ubiquitous in children in Dade County, Fla., despite the low rate of rheumatic fever and rheumatic heart disease observed in this area.

The low rheumatic rate cannot be explained by differences in groups or types of streptococci, nor by a failure of these organisms to evoke a systemic response, at least in so far as such a response is determined by antistreptolysin O rise.

Our future work is directed toward the clarification of how ultraviolet and other climatic and environmental factors may affect the defenses of the host, alter the virulence of group A beta hemolytic streptococci, and influence the interrelationship of the organism and host in regard to the pathogenesis of rheumatic fever. In order to clarify certain of these factors, a national epidemiological streptococcal study has been planned to be carried out in areas representative of different types of climate.

Summary

In a three-year study of children attending the first three grades of Dade County, Fla., public schools, throat cultures revealed that 25% to 40% of the children studied harbored group A beta hemolytic streptococci at least once during any one eight-month school year. The same groups and types of beta hemolytic streptococci were isolated as those found in the North.

Higher average antistreptolysin O titers and indices were demonstrated in the sera of those children from whose throats group A streptococci were isolated, than were observed in those from whom no beta hemolytic streptococci were recoverd.

An antistreptolysin O rise of two tubes or more occurred in 50.7% of the children with group A streptococci; only 8.6% of those children from whose throats no group A organisms were isolated had similar titer rises.

Discussion of these data is presented. The necessity for clearer definition of "infection" is emphasized, and suggested criteria for streptococcal infections are offered.

The possible effects of climate on streptococcal infections and subsequent development of rheumatic fever are considered.

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Early Diagnosis of Tuberculosis in Childhood

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There is some tendency toward reliance on clinical findings for early diagnosis of primary tuberculosis. Practitioners of both pediatrics and general medicine are guilty of this unjustified approach.

Many symptoms and symptom complexes have been mentioned. In the Scandanavian countries it has been noted that 95% of the cases of erythema nodosum are associated with tuberculosis.[1] In the United States, however, erythema nodosum occurs much oftener in association with rheumatic fever and occurs infrequently under any conditions. At a recent round-table discussion on tuberculosis conducted by the American Academy of Pediatrics, a group of approximately 35 participants was polled as to the frequency of erythema nodosum. Only one member reported the incidence of as many as two cases each year, and his residence was in northern Michigan, a climate comparable to that of the Scandanavian countries.

In the past, presence of phlyctenular conjunctivitis has been considered almost pathognomic of tuberculosis, but in recent years it has been pointed out that this disease is caused much oftener by other offending allergens than by tuberculoprotein and that tuberculosis is the causative agent in relatively few instances.

The so-called tuberculosis symptom complex consisting of chronic cough, anorexia, and failure to gain weight, or even loss of weight, is of little value, since this group of symptoms is present in a portion only of the cases of progressive tuberculous disease.

Expiratory stridor and bitonal cough, caused by compression of the bronchi, may rarely be an aid in early diagnosis of primary tuberculosis.

The fever that sometimes accompanies the development of primary tuberculosis is called initial or invasion fever. According to Wallgren,* this fever usually lasts two to three weeks but may be present less than one week or continue more than four weeks. Persistent fever, then, may arouse suspicion of tuberculosis.

Rarely, a skin lesion may be the first sign of tuberculosis.

Special Groups of Patients in the Child Chest Clinic of the Medical College of Virginia

	No. Cases
Control patients in BCG study	121
U. S. Public Health study re INH prophylaxis against tuberculous meningitis	79
Total	200

As a rule, however, the onset of primary tuberculosis is symptomless. In the Child Chest Clinic of the Medical College of Virginia there are two special groups of carefully followed patients (Table 1).† One hundred twenty-one of these are control or nonvaccinated patients in a BCG study which admits only children under 6 months of age. Another 79 are those included in the U. S. Public Health Study concerning the efficacy of isoniazid in the prophylaxis against tuberculous meningitis. Not one of these 200 cases, where tuberculous infection ranged from a positive tuberculin reaction

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From the Department of Pediatrics, Medical College of Virginia, and the Child Chest Clinic, Medical College of Virginia Hospitals.

* Reference 1, p. 124.

† Statistics as of April 12, 1956.

to widespread pulmonary disease, exhibited a single symptom or sign which could be associated with any disease process. All were diagnosed by means of a routine tuberculin test or by a tuberculin test performed because of known contact with tuberculosis.

Report of Cases

CASE 1.—An example of these cases is a Negro boy in the control group of the BCG study. At 7 months of age he was found to have tuberculous infection, as manifested by a positive Mantoux reaction. No symptoms had been noted, and physical examination revealed no pathology. X-ray of the chest showed extensive parenchymal disease (Fig. 1).

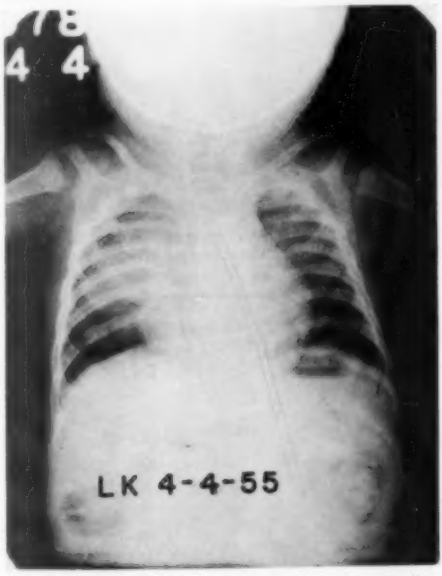


Fig. 1 (Case 1).—Extensive parenchymal disease, right lung.

It should be pointed out that many cases of so-called progressive primary tuberculosis exhibit minimal symptoms, which may easily escape the attention both of parents and clinician. Following are a few illustrative cases, the first two of which have been previously reported.‡

CASE 2.—An infant born of a mother known to have miliary tuberculosis. The baby was inadvertantly put to breast one time in the first 24 hours after delivery but was thereafter kept isolated from the mother. On the 23rd day of life the baby had a slight temperature elevation which reached a maximum of 101 F (rectal) 2 days later. There were no other symptoms, and physical examination was negative. Tuberculin patch test was positive and smear of gastric washings revealed the presence of acid-fast bacilli (Fig. 2).

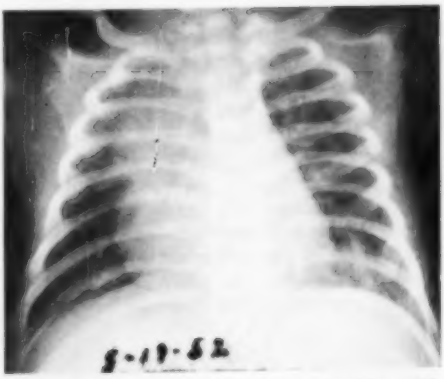


Fig. 2 (Case 2).—Heavy hilar densities with areas of increased density in left lung base. (Courtesy of American Review of Tuberculosis, National Tuberculosis Association, New York.)

The fever was a transient one, lasting only a few days, and the patient subsequently developed tuberculous pneumonia without demonstrable symptoms or signs (Fig. 3).

CASE 3.—An infant born of a mother who had tuberculosis with sputum positive for tubercle bacilli. The baby was born at home without benefit of attendance. She was kept in the same room with the mother for 10 hours, and both were carried to the hospital in the same ambulance. Upon arrival, the baby was placed in the premature unit. Her course thereafter was the usual one

Fig. 3 (Case 2).—As in Figure 2 with addition of nodular densities, right lung. (Courtesy of American Review of Tuberculosis, National Tuberculosis Association, New York.)

‡References 2 and 3.

for a premature infant until the 19th day of life. At that time it was noted that she had a temperature elevation of 100.8 F (rectal) and fever, which was later considerably higher, continued for 14 days. There were no other symptoms or signs except mild dehydration. X-rays of the chest showed widespread pulmonary tuberculosis (Fig. 4).

Case 4.—A 3-year-old Negro girl was referred to Dooley Hospital with diagnosis of pulmonary tuberculosis. There was no history of contact

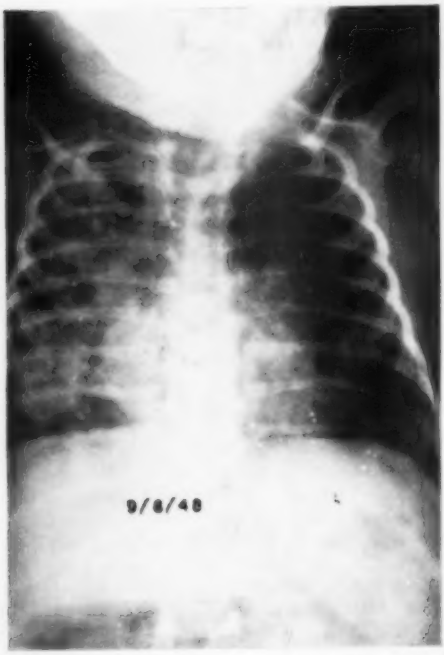


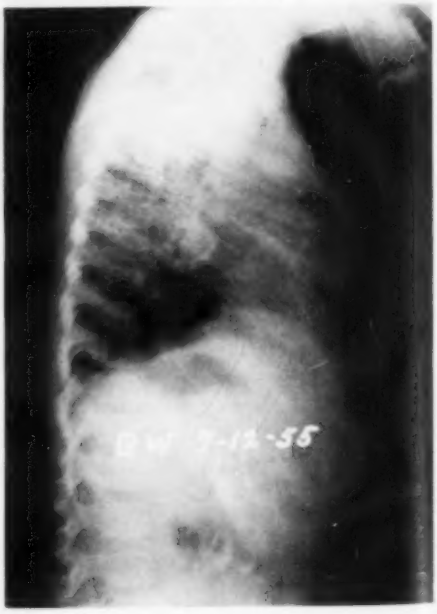
Fig. 4 (Case 3).—Widespread pulmonary disease, more extensive on right (film three weeks after diagnosis). (Courtesy of American Review Tuberculosis, National Tuberculosis Association, New York.)

with tuberculosis. The only symptoms were questionable failure to gain weight during the preceding year and tendency "to cough when taking violent exercise." Physical examination at time of admission was negative, but chest x-ray revealed atelectasis of upper lobe, right lung, a thin-walled cavity in right midlung field and miliary tuberculosis (Figs. 5 and 6).

It is apparent from the foregoing that the clinician is not justified in placing dependence on symptoms or physical signs in the early diagnosis of primary tuberculosis.

Fig. 5 (Case 4).—Atelectasis upper lobe, right lung, and miliary tuberculosis. Cavity not demonstrable.

Fig. 6 (Case 4).—Lateral view, showing thin-walled cavity right midlung field.



The indicated procedure for early diagnosis appears to be employment of the routine tuberculin test, but this is not generally utilized as might be desired. A survey conducted a few years ago among 2500 practicing pediatricians[4] in the United States, showed that among 1480 who answered the questionnaire, only 821 (55.5%) employed the tuberculin test routinely, and, of these, 174 (21%) used the test after three years of age, too late to be of maximum case-finding value.

It is suggested, therefore, that a routine tuberculin test be done sometime during the first year of life, prior to smallpox vaccination, if possible, since this is a suspected activator of tuberculous disease, and annually thereafter. Only in this way is early diagnosis of tuberculous disease in children possible. Use of the tuberculin test whenever a child has known contact with tuberculosis is, of course, mandatory.

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Hypernatremia Accompanying Infant Diarrhea

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Elevation of the serum sodium concentration has been recognized as a frequent phenomenon in the fluid and electrolyte imbalances accompanying infant diarrhea.* Its importance is indicated by the fact that the mortality rate in such cases is five times that of patients with normal or low sodium concentration.[2] Recognition of the disturbance is more difficult than the diarrheal imbalances in which salt depletion is prominent. Marked disturbances of the central nervous system occur. Fluid and electrolyte management during repair is difficult.

Our experience with patients with diarrhea and hypernatremia has led us to conclude that two mechanisms, singly or together, are the causes of the disturbance. These are (a) profound water depletion with hyperosmolarity of which the hypernatremia is a part and (b) sodium administration in excess of the excretory capacity of the kidney.

This report will present the clinical problem as manifested in a number of patients, and discuss the pathogenesis and repair of the disturbance.

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Presented in part to the Western Society for Pediatric Research, Portland, Ore., Oct. 19, 1955.

From the Department of Pediatrics, University of Washington Medical School, the Pediatric Services of the King County and Children's Orthopedic Hospitals.

* References 1-4.

Materials and Methods

Patients.—The records of all infants admitted for diarrhea to the King County Hospital and the Children's Orthopedic Hospital (380 in number) during the five-year period ending June 30, 1955, were reviewed. In 61 cases the serum sodium concentration was measured or could be inferred by summation of the measured chloride plus bicarbonate concentrations; 14 of the 61 patients had hypernatremia (Table 1). Seven of the patients were observed by the authors. In some of these fluid balance was carried out by a simple clinical method.[5]

Definition of Hypernatremia.—Hypernatremia was arbitrarily defined as a serum sodium concentration of 150 mEq. per liter or higher. This is substantially higher than the commonly accepted "upper limits" of normal.[6] When the serum concentration was inferred from adding chloride and bicarbonate, the concentration of the unmeasured serum anions ('R') was estimated as 25 mEq. per liter and the concentration of unmeasured cations as 11 mEq. per liter (Figure). In our experience with infants with diarrhea this estimate of the 'R' fraction is conservative.

Analyses.—Serum and blood analyses were performed on venous blood. Sodium and potassium analyses were done with a Baird flame photometer,[7] chloride by the method of Schales and Schales,[8] and carbon dioxide combining power by the method of Van Slyke.[9] Where indicated in the tables, the "bedside" techniques of Scribner and coworkers were used: sodium is determined by subtracting 11 mEq. from the total base concentration measured with a cation exchange resin column,[10] chloride by a mercurimetric titration,[11] and bicarbonate by a modification of the titrimetric procedure of Van Slyke.[12] Blood urea nitrogen was determined by Gentzkow's technique,[13] serum calcium by the method of Clark and Collip,[14] and inorganic phosphorus by the method of Fiske and Subbarow.[15]

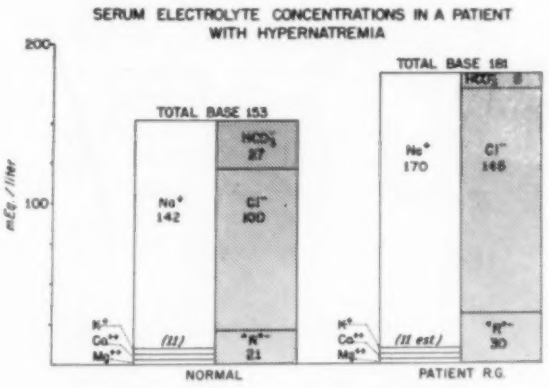
Results

The seven patients observed closely by the authors are representative of the clinical features present in cases of hypernatremia. Water and electrolyte data obtained

TABLE 1.—*Hypernatremia Accompanying Infant Diarrhea*

Case	Age	Hospital Day	Serum Electrolyte Concentrations (mEq/L.)			
			Na	K	Cl	HCO_3
1	12 mo.	1	170	5.0	145	8.0
2	8 mo.	1	178$_a$	5.0	156	5.0
3	8 mo.	1	184$_a$		168$_b$	12.0$_b$
4	10 mo.	1	170		144	7.0
5	6 mo.	1	154$_b$		83$_b$	25.0$_b$
6	6 mo.	2	180$_b$		140$_b$	21.0$_b$
7	6 wk.	1	154$_b$		130$_b$	15.0$_b$
		3	168		----	----
8	3 mo.	1	151$_a$		128	9.0
9	9 mo.	1	154$_a$		120$_b$	20.0
10	10 mo.	3	160$_b$		121	25.0$_b$
11	11 mo.	2	158	3.7	112	9.0
12	12 mo.	4	151	4.1	105	24.0
13	12 mo.	1	159$_a$		120	25.0
14	18 mo.	1	160$_b$		116	30.0

Fourteen cases of hypernatremia accompanying infant diarrhea. Where marked by the subscript "a," serum sodium concentration was estimated from summation of measured [Cl−] plus measured [HCO_3^-] plus an estimate of 25 mEq/L. for unmeasured serum anions, minus 11 mEq/L. representing [K+], [Mg++], and [Ca++] (Fig. 1). Subscript "b" indicates "bedside" methods (see text).



from the records are recorded in Table 2.

Cases 1 and 2 represent those patients in whom hypernatremia is part of the hyperosmolarity resulting from profound water depletion.

CASE 1.—This 12-month-old boy (who had weighed 10,300 gm. on a routine office visit 10 days prior to admission) had watery diarrhea for several days treated by oral medications and a diet of boiled skimmed milk and was admitted to the hospital when he failed to improve. On admission he weighed 8200 gm. and was febrile to 100.8 F (38.2 C). He appeared ill and was lethargic but responsive. He was hyperventilating. The skin was dry but the turgor was good. There were no other remarkable physical findings. Serum electrolyte concentrations were sodium, 170 mEq/liter; chloride, 145 mEq/liter, and bicarbonate, 8 mEq/liter. His parenteral fluid therapy during the first 23 hours was 1020 cc. of water containing 19 mEq. of sodium and chloride. At the end of this period he was less responsive and twitching. The serum sodium concentration was 160 mEq/liter; chloride, 139 mEq/liter; bicarbonate, 9 mEq/liter, and the blood urea nitrogen 106 mg/100 cc. Six hours later, after continued infusion of hypotonic fluids (Table 2) he developed generalized convul-

TABLE 2.—*Water and Electrolyte Data in Seven Patients with Hypernatremia*

Case No. Age Normal Weight	Period	Duration	Intake					Urine Output		Observations at End of Period						
			Water, Cc.	Sodium		Cl, mEq.	K, mEq.	Water, Cc.	Cl, mEq.	Wt. Kg.	Serum Electrolyte Concentrations, mEq. per Liter				Other Lab.	Comment
				mEq.	mEq/Kg/Day						Na	Cl	K	HCO_3		
1	...	...	.....	.....	.....	.....	.....	.....	.....	8.2	170	145	5.0	8.0	.....	Admission data
12 mo. 10.3 kg.	1	23	1,020	19	1.9	19	0	?	?	9.0	160	139	4.7	9.0	BUN 106 mg%	
	2	6	680	7	2.7	7	0	25+	?		159	132		6.0		Onset of convulsions
	3	18	870	33	4.5	5	5	385	17	9.0	143	112	3.4	19.0	BUN 84 mg%	Coma, apnea, edema, hepatomegaly
	4	24	1,125	3	0.3	27	27	1,130+	45		144	108		21.0	BUN 30 mg%	Paralysis
2	...	...	.....	.....	.....	.....	.....	.....	.....	8.5	176$_b$	156	6.0	5.0		Admission data
8 mo. 8.7 kg.	1	14	510+	30	3.5	20	4	25	?	8.7	169	155		7.0	BUN 96 mg%	Edematous
	2	24	810	7	0.8	7	11	180	?	8.7	164	145	5.2	13.0		In O_2
	3	24	?	?	?	?	?	?	?	?	154	133	4.1	11.0		Facial palsy, weakness
3	1*	48*	5,000*	300*	18*	300*	?	++++*	?	8.6	184$_a$	168$_b$		12.0$_b$		Admission data; *shows data estimated from home therapy history
8 mo. 8.35 kg.	2	8	833	61	22	46	1	15	?		192	155$_b$		12.0		Salicylates, 17 mg%
	3	20	667	0.7	0.1	0.9	5	410	113		176	115	2.8	12.0		Edema, death

Subscript "a" indicates serum sodium was estimated from summation of measured [Cl-] plus measured [HCO_3] plus an estimate of 25 mEq/L. for serum anions, minus 11 mEq/L. representing [K+], [Mg++], and [Ca++]. Subscript "b" indicates "bedside" methods.

TABLE 2.—*Water and Electrolyte Data in Seven Patients with Hypernatremia*—Continued

Case No. Age Normal Weight	Period	Duration	Intake					Urine Output		Observations at End of Period						
			Water, Cc.	Sodium		Cl, mEq.	K, mEq.	Water, Cc.	Cl, mEq.	Wt. Kg.	Serum Electrolyte Concentrations, mEq. per Liter				Other Lab.	Comment
				mEq.	mEq/Kg/Day						Na	Cl	K	HCO_3		
4 10 mo. 8.4 kg.	1	48	2,500*	150*	8.9*	150*	?	?	?	8.5	179	144		7.0		* Indicates data estimated from history of home therapy; admission data
	2	20	595	14	2.0	14	0	295	65		157	119	4.6	14.0		
	3	24	1,125	43	5.1	13	4	160	26							
	4	24	1,135	58	6.9	14	5	750			150	93	2.7	30.0		
5 6 mo. 8.7 kg.	1	16	700	108	16.2	62	2	?	?	8.39 8.42	154b	83b		25b		Admission
	2	24	1,780	154	17.7	109	30	?	?	9.23						
	3	5	100	15	8.3	15	0									
	4	9	500	0	0.0	0	0				149b	111b		23b		Convulsed
	5	10								8.86						
6 6 mo. 8 kg. (est.)	1*	12*	500*	77*	19.3*	77*	0*	0*	0*	7.64		114		9		*Clysis given in another hospital; admission values
	2	24	1,175	148	18.5	108	1	65	?		180b	140b		31b	BUN 97 mg%	
	3	19	85	4	0.5	0	0	60	3	8.25	173	118	3.5	12	BUN 102 mg%	
	4	16	380	0	0.0	0	0	85	4	8.34	165	107		8		Anasarca, death

Subscript "a" indicates serum sodium was estimated from summation of measured $[Cl^-]$ plus measured $[HCO_3]$ plus an estimate of 25 mEq/L. for serum anions, minus 11 mEq/L. representing $[K^+]$, $[Mg^{++}]$, and $[Ca^{++}]$. Subscript "b" indicates "bedside" methods.

TABLE 2.—*Water and Electrolyte Data in Seven Patients with Hypernatremia*—Continued

Case No. Age Normal Weight	Period	Duration	Intake					Urine Output		Observations at End of Period						
			Water, Cc.	Sodium		Cl, mEq.	K, mEq.	Water, Cc.	Cl, mEq.	Wt. Kg.	Serum Electrolyte Concentrations, mEq. per Liter				Other Lab.	Comment
				mEq.	mEq/Kg/Day						Na	Cl	K	HCO_3		
7 6 wk. 4.5 kg. (est.)										2.86	154_b	130_b		15_b		Admission values
											145_b	123		16		After 11 hr. of period 1
	1	23	620	53	12.9	48	8	+++	?							
	2	24	530	13	2.9	4	4	++	?	3.04	160	121	2.9	19		
	3	24	692	26	5.7	17	8	28+	?		168		3.3			
	4	14	269	7	2.8	5	6	45	12	3.49						Edema
	5	11	120	0	0.0	5	5	30	?	3.64						
	6	23	595	8	1.9	8	14	100	?	3.56	142					
	7	24	650	11	2.5	11	19	+++								Skimmed milk
	8	24	650	11	2.5	11	19	+++								Skimmed milk
	9-13 each	24	500-885	9-16	2-3.6	9-15	15-27	+++	?	3.69-3.93	--	--	--	--	----	Persistent edema; fortified skimmed milk

Subscript "a" indicates Serum sodium was estimated from summation of measured [Cl −] plus measured [HCO_3] plus an estimate of 25 mEq/L. for serum anions, minus 11 mEq/L. representing [K+], [Mg++], and [Ca++]. Subscript "b" indicates "bedside" methods.

sions which continued despite the administration of calcium gluconate and phenobarbital. The skin was found to be dry and doughy. Because of the continued low serum bicarbonate concentration and an erroneous report of a remarkably low serum pH, a considerable amount of sodium as sodium lactate was included in the fluid therapy of the next 18 hours (Period 3, Table 2). During this time his weight remained stable, the sodium concentration fell to 143 mEq/liter, and the bicarbonate concentration rose to 19 mEq/liter. The patient continued to twitch slightly and then developed coma and then apnea. He was placed in a tank respirator and was ventilated artificially for nine hours. Edema and hepatomegaly became apparent. He then reestablished spontaneous and adequate respiratory activity but had generalized flaccid paralysis. This gradually resolved, the left side clearing considerably before the right. Several months after the illness his only neurological abnormality was a slight divergent strabismus.

Summary.—This one-year-old boy entered with water depletion due to diarrheal losses, with a serum sodium concentration of 170 mEq/liter. Other than loss of weight, he showed little evidence of fluid disturbances. His hospital course was marked by profound neurological disturbances from which he ultimately recovered.

Case 2.—This 8-month-old boy developed diarrhea and vomiting which continued for 6 days prior to admission despite antibiotic and other medications. He became weak, tachypneic, and was admitted because of increasingly severe illness and weight loss. On examination he weighed 8470 gm., had a temperature of 101.3 F (38.5 C) rectally, a pulse rate of 190, and a respiratory rate of 80. He was described as acutely ill and "exhausted." The skin was dry and of poor turgor, the tongue volume was diminished. Neurological examination showed marked weakness and absence of deep tendon reflexes. The physical examination was not otherwise remarkable. Urinalysis showed a large number of granular and hyaline casts and the presence of albumin. Blood was obtained for electrolyte determinations and his physician ordered an initial solution containing 60 cc. of 1/6 M. sodium lactate, 120 cc. of isotonic saline, and 180 cc. of 5% dextrose in water given intravenously. When the serum total base was reported as 187 mEq/liter, chloride 156 mEq/liter, and bicarbonate 5 mEq/liter, all intravenous therapy was discontinued and he was offered glucose water and boiled skimmed milk by mouth. On the day after admission the child had periorbital edema and was receiving oxygen because of tachypnea. Cultures of the nasopharynx showed Staphylococci coagulase-positive and Friedländer's bacillus; blood cultures showed no growth. Over the succeeding six days he was febrile despite antibiotic therapy, remained semiconscious, had periorbital puffiness, and was thought to be thirsty by the nursing personnel. Thereafter he became afebrile but remained inactive in bed. A right facial weakness was found on the third hospital day but had cleared by the day of discharge. After gradual improvement he was discharged weighing 8700 gm., with persistent weakness and lethargy. On a follow-up visit to the outpatient department several weeks later he had improved markedly and seemed to the mother and examiner to have the motor activity and developmental pattern of a normal child of his age.

Summary.—This 8-month-old boy had diarrhea resulting in both salt depletion (manifested by poor skin turgor, shrunken tongue) and water depletion (manifested by dry skin, severe neurologic disturbances, and elevation of the serum total base to 187 mEq/liter). No residual neurological damage was found several weeks after discharge.

In Case 3 hypernatremia occurred as a result of the administration of a large intake of sodium.

Case 3.—This 8-month-old boy developed otitis media 4 days prior to admission for which he was treated by his physician with penicillin. Later that day he developed profuse, watery diarrhea. This continued, and two days before admission he was again seen by the physician who advised oral remedies including salt water prepared by adding one teaspoon of table salt to a quart of water (reproduction of this method of preparation using household teaspoons of varying size produced sodium concentrations of 75 to 125 mEq/liter). The child took about four quarts of this solution and additional water during the next two days. The urine volume remained good. He was febrile throughout the illness. He was referred to the hospital because of increasing fever and diarrhea.

On admission he weighed 8600 gm. (he had weighed 8350 gm. immediately prior to the onset of the diarrhea) and was febrile to 102.2 F (39 C). The pulse rate was 160 and the respirations 76 per minute. He was lethargic and acutely ill. The lips, mucosa, and nailbeds were cyanotic. The skin was dry, but the turgor was not diminished. No edema was apparent. Rales were heard at both lung bases. Other than injection of both tympanic membranes, no other abnormal findings were noted.

Presumptive diagnoses of metabolic acidosis and dehydration due to diarrhea were made. Venous blood was drawn for serum electrolyte determinations and parenteral solutions were started by clysis and through a saphenous cut-down. (Table

2, Period 2). The admission electrolyte concentrations showed chloride, 168 mEq/liter and bicarbonate, 12 mEq/liter. Six hours after admission the serum sodium concentration was found to be 192 mEq/liter; chloride, 155 mEq/liter, and bicarbonate, 12 mEq/liter. The child at this time was somnolent and still hyperventilating. The history of salt ingestion was then obtained from the mother. Urine collections by catheter were instituted and an attempt was made to remove fluid and electrolyte by gastric suction and lavage. Further fluid therapy is recorded in Table 2, Period 3. Twenty-three hours after admission, edema was noted. He remained somnolent, developed more marked cyanosis, became areflexic and apneic, and died 33 hours after admission.

Postmortem examination by Dr. S. Allison Creighton revealed as the only abnormal findings, pulmonary edema and areas of patchy pneumonia. (Microscopic examination of the brain was not done.)

Summary.—This child was treated for diarrhea with large amounts of oral saline. Despite adequate water intake and maintenance of his urine volume, he developed hypernatremia and edema and died.

In cases 4, 5, 6, and 7 water depletion and sodium administration both seem to have contributed to the development of hypernatremia.

CASE 4.—This 10-month-old girl developed projectile vomiting and diarrhea 6 days prior to admission. Oral intake was restricted to boiled skimmed milk but the diarrhea continued at a rate of 10 to 20 watery stools daily. Three days prior to admission she was seen by a physician who prescribed an oral remedy and administered penicillin; the diarrhea continued. Two days prior to admission the mother noted listlessness, sunken eyes, and that the skin wrinkled when pinched. Another physician was consulted who advised a regimen consisting of thin gruel every 2 hours and 2 oz. of liquid every 15 minutes, alternating plain water and salt solution made by adding one teaspoon of salt to a quart of water. The diarrhea continued. The skin improved, but the child became sicker and was referred to the Children's Orthopedic Hospital.

On admission she weighed 8500 gm. and was febrile to 102 F (38.9 C) rectally. The pulse rate was 140, respiratory rate 48 per minute. She was acutely ill and lethargic, but responded to stimulation with an irritable cry. The skin was dry and doughy, but the elasticity was normal. The oral mucosa was dry. Physical examination was not otherwise remarkable.

Blood was drawn for serum electrolyte determinations which showed a sodium concentration of 179 mEq/liter; chloride, 144 mEq/liter, and bicarbonate, 7 mEq/liter. No diarrheal stools were passed after admission. The fluid and electrolyte therapy and the subsequent laboratory determinations are tabulated. The course was one of gradual improvement and was marked by weight gain to 8790 gm. on the fourth day followed by a fall in weight to 8400 gm. on the seventh day. She was discharged entirely well.

Summary.—This infant had received a moderately large amount of sodium chloride per os for diarrhea prior to admission to the hospital. Clinical findings included lethargy, irritability, and doughy and dry skin with normal elasticity. Her serum sodium concentration on admission was 179 mEq/liter. She recovered uneventfully with slow administration of hypotonic fluids.

CASE 5.—This 6-month-old girl entered the hospital with a history of 3 days of watery diarrhea and one day of fever. She had been treated with antibiotics and restriction of the diet to boiled skimmed milk. On examination she weighed 8390 gm. She was febrile, obese, pale, and irritable. The pulse rate was 100, respiratory rate 24. There was no apparent loss of skin turgor or moisture, or any other abnormal physical finding. A small amount of urine and explosive watery stools were passed during the examination. No serum electrolyte determinations were obtained on admission. Oral feedings were withheld and she was given isotonic parenteral solutions subcutaneously with hyaluronidase (Table 2). On the morning after admission serum electrolyte determinations were done by the bedside methods and showed total base of 165 mEq/liter; chloride, 83 mEq/liter, and bicarbonate 25 mEq/liter. Isotonic solutions were continued by clysis, and oral boiled skimmed milk was fed. After 42 hours hospitalization she had a rectal temperature of 105.8 F (41 C) and was having frequent watery stools but had gained almost 900 gm. She was irritable with dry and slightly doughy skin but normal turgor. The tongue volume was normal. The thighs were puffy at the clysis sites. The urine volume appeared small. At this time a review of the previous electrolyte concentrations, the therapy thus far, and the clinical findings suggested the probability of hypernatremia and a saphenous cut-down was done, through which 500 cc. of 5% dextrose in water was infused over the succeeding nine hours. She then developed generalized twitching movements during which she voided a large quantity of urine into the bed. Five cc. of intravenous 10% calcium gluconate

and 30 mg. of intramuscular phenobarbital were given without immediate effect, and serum electrolyte determinations were done showing chloride, 14 mEq/liter; bicarbonate, 33 mEq/liter, and total base, 160 mEq/liter. The convulsions slowly subsided while the infusion was maintained at the same rate. She voided frequently. A lumbar puncture revealed no abnormality other than a chloride concentration of 142 mEq/liter. The following day she was improved and had lost weight to 8860 gm. Her further course was uneventful and she went home well after seven days in the hospital, weighing 8700 gm.

Summary.—This infant entered with diarrhea and weight loss but no other physical findings indicating salt depletion or water depletion. The initial therapy consisted of isotonic solutions. After 16 hours, doughy skin and irritability were found and the total base concentration had risen to 165 mEq/liter. A convulsion occurred after hypotonic fluids were started. Recovery was otherwise uneventful.

CASE 6.—This 6-month-old girl developed watery diarrhea and vomiting 5 days prior to admission which continued until she was seen. During the day prior to admission she became acutely ill with fever to 102.2 F (39 C) rectally, somnolence, oliguria, and anorexia. The family physician found her semicomatose and admitted her to another hospital where she was given 500 cc. of 5% dextrose in saline subcutaneously and then transferred to The Children's Orthopedic Hospital. Examination showed a somnolent infant weighing 7640 gm. with temperature 100.4 F (38 C), respiratory rate 50, pulse 150. The skin was "rubbery," cold, and dry. The tendon reflexes were hypoactive. No other abnormality was noted, except that the clysis site over the right aspect of the trunk was puffy. Serum electrolyte concentrations were chloride, 114 mEq/liter; bicarbonate, 9 mEq/liter. A blood culture was drawn and later reported as showing no growth. The child was given a rapid infusion of one-sixth molar sodium lactate followed by a mixture of Ringer's lactate and dextrose water. Penicillin was given by injection and triple sulfonamides (sulfadiazine, sulfamethazine, and sulfamerazine) by mouth. She remained somnolent but occasionally cried when disturbed, and sucked eagerly at the spoon when given medications. Oliguria persisted. The morning after admission she had facial edema, shallow respirations with expiratory prolongation, and seemed worse. Serum electrolyte determinations showed an elevated serum sodium concentration. Another blood specimen was taken, and the elevation was confirmed with a total base of 191 mEq/liter. Fluid restriction was instituted but generalized edema became apparent. During the second night in the hospital her respirations became grunting and she developed generalized rigidity. She later developed pulmonary edema, which did not respond to lanatoside C U. S. P. XIV (Cedilanid) and oxygen, and died.

Postmortem examination by Dr. S. Allison Creighton showed anasarca, pulmonary edema, edema of the brain, hepatomegaly, and petechial hemorrhages over the surface of both kidneys. Microscopic findings included diffuse pneumonitis, cloudy swelling and fatty metamorphosis of the liver, and granular degeneration of the adrenal cortex. There was cloudy swelling of the renal tubular cells but no necrosis or disruption of the basement membrane. Microscopic examination of the brain was not done.

Summary.—This infant had a severe disturbance with coma, hypoactive tendon jerks, and "rubbery" skin present on admission. The initial fluid therapy was rich in sodium; after 36 hours of therapy serum total base concentration was 191 mEq/liter. She died with generalized anasarca.

CASE 7.—This 6-week-old boy whose birth weight had been 3600 gm. was admitted with a history of watery diarrhea for four days. He had refused feeding for three days but had not been febrile. Physical examination on admission showed an acutely ill, afebrile, listless infant with a weak cry. The skin and mucosa were dry, the anterior fontanelle was sunken, and the skin turgor was poor. He appeared undernourished and weighed 2870 gm. There were no other apparent abnormalities. Bedside electrolyte determinations showed total base 165 mEq/liter, chloride 130 mEq/liter, bicarbonate 15 mEq/liter. Diagnoses of water depletion, salt depletion, and metabolic acidosis were made. The elevated serum cation concentration was recognized, but repair of the salt depletion indicated by the poor turgor and other signs was thought desirable. A polyethelene catheter was placed in a saphenous vein and parenteral therapy was instituted as tabulated. There was a definite and immediate improvement in color and alertness, and the patient voided within the first four hours and several times later that day. The diarrhea stopped. The next day he was improved, and on the morning of the third day he appeared to be doing well. Serum electrolyte determinations drawn that morning were not reported until late in the day, and the sodium concentration was 160 mEq/liter. An oral preparation containing electrolytes and calories was given. The morning of the fourth day found him edematous, and another determination of the serum sodium concentration revealed a level of 168 mEq/liter. The situation

was reviewed and oral therapy was discontinued. Intake was limited to glucose water until the following afternoon when half-strength skimmed milk was started. Edema was no longer apparent. This formula was increased to full strength skimmed milk and on the ninth day skimmed milk solids were added because of an exacerbation of diarrhea. The edema again was found. On the 14th day the formula was again changed to a modified skimmed milk-whole milk product. Solids were later added. Edema was still found until the 17th hospital day. His weight on discharge was 4320 gm. at 9 weeks of age.

Summary.—This 6-week-old boy entered with physical findings indicative of salt depletion (poor skin turgor, sunken fontanelle) and water depletion (dry skin and mucosa, serum total base 165 mEq/liter.) The initial therapy lowered the total base concentration to 156 mEq/liter; however, the subsequent feeding per os of solute-rich formulas (skimmed milk plus skimmed milk solids) and oral electrolytes resulted in persistent hypernatremia and edema.

Clinical Observations

The common historical findings in the foregoing cases may be listed as follows:

1. All patients had profuse, prolonged, watery diarrhea.
2. Some of the patients had fever.
3. In all cases the caloric intake was subnormal because of anorexia or alteration of the formula to boiled skimmed milk.
4. Most patients received moderate or large amounts of sodium per os or parenterally.

On physical examination only two of the seven patients had overt evidence of reduction of the volume of the extracellular space as manifested by poor skin turgor, sunken fontanelle, sunken eyes, etc. (Table 3). Most had lost weight to a degree in excess of their obvious "dehydration." The skin and mucosa were dry. In some the skin was described as "doughy" or "rubbery." Periorbital or pitting edema was not apparent initially in any patient. Edema appeared in two patients whose repair included large amounts of sodium and in three others whose repair included much smaller amounts of sodium as the serum sodium concentration fell in response to administration of dilute fluids.

Alterations in neurologic findings were present in most cases. All were lethargic. Most were irritable when handled. The deep tendon reflexes were hypoactive in one case and absent in two others. Four were somnolent on admission, and three of these became comatose. Muscular rigidity occurred in two patients, one of whom also showed hyperactive tendon reflexes. Two became apneic; one died, and the other required artificial ventilation. Convulsions occurred in two patients while being given hypotonic solutions.

Comment

In the discussion to follow we will define alterations in the volume and concentration of the body fluid compartments according to the terminology of Marriott,[16] Darrow and Yannett,[17] and Scribner.[5] Alterations in the volume of the extracellular compartment are called "salt excess" or "salt depletion" because of the role of sodium in maintaining this space. Disturbances of volume distributed throughout the total body water are called "water excess" or "water depletion." The clinical and laboratory criteria for the diagnoses of salt depletion and water depletion are outlined in Table 3. Edema is overt evidence of salt excess.

Pathogenesis of Water Depletion.—In these patients several factors contributed to the development of water depletion resulting in hyperosmolarity and hypernatremia.

A. Dilute Diarrheal Stools: Stool losses in diarrhea may range from 100 to 555 cc. daily.† The sodium concentration may range from 19 to 104 mEq. per liter of stool water.‡ The data suggest that an infant whose diarrheal stool has a high sodium concentration will show relatively more salt depletion than water depletion, whereas the infant with a low stool sodium concentration will develop relatively greater water depletion.

†References 18, 19, and 20.
‡References 4, 19, and 20.

TABLE 3.—*Differential Diagnosis of Salt and Water Depletion*

	Salt Depletion	Water Depletion
Fluid Compartment Affected	Extracellular	Total Body Water
Symptoms		
Thirst	Absent	Marked
Vomiting	Frequent	Absent
Weight Loss	Apparent, moderate	May be marked, but inapparent
Physical Findings		
Blood Pressure	Reduced	Normal until terminal
Skin	Inelastic, normal moisture	Dry, normal elasticity, may be doughy
Eyes, Fontanelle	Sunken	Normal
Tongue	Small, wrinkled	Normal size, dry
Neurological	Alert, anxious, "shock-like"	Lethargic, irritable, muscular irritability, convulsions
Laboratory Findings		
Urine		
Specific Gravity	Variable	Elevated
Chloride Concentration	0-35 mEq/L.	Usually above 35 mEq/L.
Hematocrit	Elevated	Normal
Serum Sodium	Low or normal	Slight to marked elevation
Mechanism of Death	Circulatory collapse	CNS disturbance*

Modified after Marriott (14)

B. Insensible Water Losses: In the healthy infant losses through the skin and lungs are on the order of 40 cc. per kilogram of body weight per day.[21] In diarrheal disease losses as high as 138 cc/kg/day have been measured. Increases in these losses in response to elevated environmental temperature[22] and hyperventilation[23] have been demonstrated.

C. Reduced Water Intake: Anorexia and vomiting may accompany infant diarrhea. In addition, some of these patients, despite thirst, were fed only solute-rich preparations.

D. Increased Renal Water Requirement: The starving person requires a greater amount of water for excretion of urine solute than does the person on a normal diet or one whose caloric need is partly met by glucose.§ Butler and co-workers in the same studies also showed that when glucose is given to the starved person three days or more are required for the renal solute output to drop to the level which determined the "minimum renal water requirement." Fever and illness increase metabolic activity and the caloric need; a proportionate increase in the solute produced by catabolism may be anticipated in the starved infant. The renal water requirement of such infants has not been measured, but it is probably higher proportionately than that of adults.

Some of the infants continued to feed but were fed skimmed milk, and in one patient the milk was enriched with skimmed-milk solids. Such formula is high in solute in proportion to calories and has been shown to increase the renal water requirement.[26]

Many studies have shown that the infant has limited concentrating ability when compared with the adult.‖ An increase in the renal water requirement is a corollary to this demonstration.

The Role of Impaired Renal Function.—Oliguria and nitrogen retention have been known to accompany fluid and electrolyte imbalances in infants for some years. Calcagno and Rubin¶ have shown (a) that "dehydration" with salt depletion due to diarrhea causes reduction in glomerular filtration and renal plasma flow, and also (b) that simple water restriction will also cause these changes in renal function. Water depletion does not cause such changes in the adult until it is marked. These findings indicate different mechanisms in the response of infants and adults to water depletion.

§References 24 and 25.

‖References 27-30.

¶References 31 and 32.

Where the adult increases the water reabsorption in the distal tubule, the infant responds also by reducing his renal blood flow and glomerular filtration and in this respect acts more like a reptile [33] than like an adult mammal.

The implication is that the infant is less able to defend himself against hypernatremia and hyperosmolarity in that less solute is filtered into the tubule for possible excretion.

Pathogenesis of Salt Excess.—Many authors have discussed the retention of sodium by the sick or postoperative patient. A variety of figures have been presented from adult figures for the "ceiling" for renal sodium excretion. Elman and co-workers [34] have placed the ceiling at less than 100 mEq. per day. On the basis of adult data Talbot, Crawford, and Butler [35] elected to estimate the upper limit of sodium tolerance as high as 250 mEq. per square meter of body surface area per day (approximately 400 mEq/day for the average adult, and equivalent to 11.5 to 12.5 mEq/kg/day for a 5 to 10 kg. infant). There is obviously variation not only in the findings of various investigators but in the renal sodium ceiling from patient to patient and from circumstance to circumstance.

The renal response of healthy infants and adults to infusions of sodium has been studied. Dean and McCance [36] found that hypertonic saline infusions caused in adults a prompt rise in the excretion of water and salt; in contrast, the infants showed a response slow to develop and trifling in amount. Leaf and Couter [37] demonstrated that the administration of 480 mEq. of sodium as sodium chloride or sodium citrate to adult subjects was accompanied by a rise in urine sodium output until the output equalled the input on the third day. In contrast, Gamble and co-workers [38] administered 10 millimols of sodium per kilogram of body weight per day to normal infants as the chloride or bicarbonate salt and found accumulation of sodium almost to the end of the eight-day periods of load. (For purposes of comparison, the loads given the adults were approximately 275 mEq. per square meter of surface area per day, and those given infants were about 200 mEq. per square meter per day). Thus it seems established that the normal infant is less able than the adult to excrete a sodium load, even when in good health.

In examining the protocols of patients presented here, it is seen that patients 3, 4, 5, and 6 received sodium at a rate of 22, 9, 19, and 19 mEq/kg/day, respectively. The higher figures by any criteria exceed the excretory mechanisms of even the healthy infant. Patient 7, the youngest patient in this series, developed hypernatremia and edema while receiving approximately 3 to 5 mEq/kg/day in relatively high solute feedings. It is suggested that the sodium ceiling must vary with the amount of total solute presented to the kidney for excretion.

Experience with these and other patients who have developed salt excess has led us to conclude that the ceiling for renal excretion of sodium may be in the range of 5 to 10 mEq. per kilogram of body weight per day. Therefore the use of sodium-containing solutions for the treatment of metabolic acidosis or for expansion of the circulatory volume in patients without clinical evidence of salt depletion should be undertaken with caution.

Diagnosis and Treatment.—In our experience approximately one out of four infants with moderately severe or severe imbalances due to diarrhea will have elevation of the serum sodium concentration. The diagnosis is suggested when the history indicates factors conducive to water depletion, when there has been weight loss without the clinical signs of salt depletion, and when the physical signs listed in Table 3 are present. Hypernatremia due to salt excess is suggested when therapy for water depleted patients has included sodium in amounts exceeding 10 mEq/kg/day. The diagnosis is confirmed by the demonstration of a high serum sodium concentration or when the chloride plus bicarbonate plus 25

is greater than 160 mEq/liter. Determination of the serum total base concentration[10] is a simple procedure when the laboratory is not equipped with a flame photometer.

Repair of the disturbance is difficult. Rapid alteration of the hyperosmolar state toward normal may be accompanied by convulsions suggestive of water intoxication. The use of large amounts of alkali aimed at an accompanying acidosis seems to potentiate the metabolic derangement accompanying the water depletion and hypernatremia, and may produce edema and circulatory embarrassment. We do not agree that dilute multiple electrolyte solutions can be used employing rules of thumb for the rate of administration. Therapy must be tailored to the needs and situation of each patient. For practical purposes such patients should be assumed to be in a state of renal decompensation.

We have used on a trial basis a therapeutic plan developed as follows:

(*a*) Water administration should provide for insensible losses (about 50 cc/kg/day, or 75 cc/kg/day if febrile or hyperventilating) and cover stool losses according to the observer's estimate of their volume. Urine volume should be measured, and water may be allowed for urine according to the output of the previous period. In addition to the allowances for observed and obligatory water loss, a small additional increment of 10 to 20 cc/kg/day of water may be given to initiate repair of water depletion and permit gradual restoration of normal serum concentrations.

(*b*) Sodium administration must be sharply limited, particularly if edema is present. No renal sodium excretion can be expected in the oliguric patient. When renal function returns, 2 to 3 mEq/kg/day may be considered the middle of the range of renal adjustment. An additional allowance of 2 to 7 mEq/kg/day is ordinarily given for repair of salt depletion, but this should be less in the hypernatremic patient.

(*c*) Potassium administration should be deferred until good renal function returns. Calories are needed to reduce the solute load presented for excretion, but it cannot be expected that a substantial reduction will occur promptly. The effect of therapy can be followed by repeated determinations of serum electrolytes; the bedside techniques are most useful. Frequent determinations of body weight provide valuable information of change in the total body water. A simple clinical water and electrolyte balance procedure such as that of Scribner[8] is of great value.

Summary

Patients with hypernatremia associated with the fluid and electrolyte imbalances of infant diarrhea are presented. The disturbance occurs (*a*) in patients who develop water depletion due to losses in stool and insensible losses and to the high renal water requirement of infants, and (*b*) because of sodium administration in excess of the excretory capacity of the kidney.

Clinical features include marked weight loss despite little or no evidence of loss of extracellular volume. The skin may be doughy and is dry. The patients are lethargic and may show profound neurologic changes, including coma, apnea, abnormal tendon reflexes, muscular rigidity, and convulsions. Rapid dilution of the hyperosmolar state may cause signs consistent with water intoxication. Edema may occur.

Laboratory confirmation of the diagnosis can be obtained by measure of the serum sodium concentration by flame photometry or with a "bedside" determination of the serum total base concentration or by summation of measured anions.

The disturbance is present in approximately one out of four infants with moderately severe or severe imbalances due to diarrhea. While water depletion is the chief cause, the administration of excessive sodium in repair solutions may be responsible.

Review of the pathogenesis of the disturbance in these patients and of the pertinent literature suggests that the renal ceiling for sodium excretion in infants with

fluid and electrolyte imbalances may not exceed 5 to 10 mEq. per kilogram of body weight per day.

Optimum management during repair has been achieved by treating the patients as if in acute renal failure and proceeding slowly with allowances to cover current losses plus small additional increments for repair.

Dr. S. Allison Creighton provided reports of postmortem findings in cases 3 and 6. Miss Loretta Botto and Miss Virginia Kellogg facilitated the review of the cases, and Drs. Walter B. Seelye, Belding H. Scribner, Thomas H. Shepard, and others gave criticism of the report.

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Unilateral Multicystic Renal Disease of the Newborn

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Unilateral multicystic disease is rare, but its recognition is important because surgical treatment is so satisfactory even in infants. It must be differentiated from the other forms of renal cystic disease, that is, bilateral polycystic disease or solitary cysts of the kidney.*

Review of the Literature

Bugbee and Wollstein [6] studied the urinary tract of 4903 infants at necropsy and found a total of only four cases of unilateral cystic renal disease, an incidence of 0.1%. In the same study 11 bilateral cystic kidneys were found, 0.2%.

The present knowledge of the pathogenesis of these disorders is scant and theoretical. It is known, however, that the ureteral bud (which is derived from the Wolfian duct) as it ascends from the pelvis to form the collecting system of the permanent kidney must unite with the nephrons of the metanephrons. The most widely accepted theory concerning the origin of the polycystic and the multicystic kidney, is that of Hildebrandt. His theory, formulated in 1894, assumes incomplete fusion of the terminal elements of the ureteral bud and the tubules of the kidney. When the nephrons cannot dispose of their fluid content, cystic atrophy occurs. Kampmeir and later Davis have questioned this theory and have attributed the formation of cysts to incomplete involution and subsequent cystic degeneration of earlier mesonephric tubules. Lambert [7] reconstructed two infant polycystic kidneys and found that the formation of cysts could be attributed to primary degeneration of the metanephric nephrons. In the polycystic kidney a normally developed ureter is usually found, whereas in the multicystic kidney an atresic ureter is frequent (Table 1).

TABLE 1.—*Relationship of Atresia of Ureter to Multicystic Kidney*

Authors	Total Number of Reported Cases	Total Number of Atresic Ureters
Spence [8]	4	3
Ravich and Sanford [9]	4	4
Schwartz [10]	1	0
Campbell [11]	1	1
Willson-Pepper and Slade [12]	1	0
Weinberg, O'Connor and Senger	3	2
	14	10

It would seem from this correlation of rudimentary ureter and multicystic kidney that the Hildebrandt theory of nonunion of nephrons and ureteric anlage would be the most likely. In the previously reported cases, as in our cases, large tubular cysts can be seen in the kidney that do not connect to excretory tubules.

Comment

Unilateral multicystic kidney is a relatively large renal mass that causes severe

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* References 1-5.

gastrointestinal symptoms because of pressure on the adjacent bowel. Unless the mass is removed promptly, inanition results. There is usually no difficulty in making a diagnosis of an abdominal mass, since the mass is readily visible, palpable, and easily transilluminated.

Some confusion may exist in the differential diagnosis of bilateral polycystic disease and unilateral multicystic disease of the newborn. Since polycystic disease is invariably bilateral, there is some hesitancy in permitting a nephrectomy (for unilateral multicystic disease) in a patient in whom the other kidney may be already riddled with cysts. However, bilateral polycystic disease of the newborn is an acute fulminating disease; the majority of patients are dead within three months. There are frequently other multiple congenital defects, especially those of the brain or spleen. Renal failure is the inevitable result of bilateral cystic degeneration of the kidneys. On the other hand, the infant with a unilateral multicystic kidney usually has no other congenital abnormalities. The unilateral multicystic kidney has no discernible renal function, whereas its mate visualizes normally. As stated, the prognosis in this disease is good, if nephrectomy is carried out before inanition results. Patients have been known to have long survival periods after removal of the unilateral cystic kidney. In other patients the multicystic kidney did not form a symptom-producing mass; hence, the diagnosis was made after infancy, proving that the remaining solitary kidney provides enough renal parenchyma to maintain health. Table 2 gives the reported cases of long-term survival.

TABLE 2.—*Unilateral Multicystic Kidney Discovered After Infancy*

Authors	Age of Patient at Time of Diagnosis
Wilson-Pepper and Slade[11]	7 yr.
Mixter[11]	4 yr. 21 yr. 70 yr.
Howe and Hill[11]	13 yr.

Confirmation of the diagnosis can be made by intravenous urography. A plain film of the abdomen will show a large mass with a typical ground-glass appearance filling one entire side of the peritoneal cavity. The intestinal viscera will be seen displaced to the other side. After intravenous injection of the radiopaque dye, only the opposite kidney will visualize, and that, normally.

The three case histories to be presented have several points in common:

(1) Large palpable unilateral mass
(2) Severe gastrointestinal symptoms leading to inanition
(3) Roentgen examination disclosing evidence of a large mass in the abdomen with nonvisualization of the kidney on the affected side
(4) Excision of the mass resulting in resolution of symptoms with recovery.

Report of Cases

CASE 1.—A boy was born on May 21, 1954. Almost from birth the baby was unable to retain his feedings and began showing evidence of dehydration, elevation of temperature, and lassitude. A large mass could be papated in the abdomen. Transillumination indicated liquid contents. Laboratory data were noncontributory. The urea N was 18 on the third postnatal day. A plain film of the abdomen showed the large mass displacing the intestinal tract to the right. The right kidney visualized, and contrast media could be seen in the bladder five minutes after intravenous injection of the dye (Fig. 1). By the sixth postnatal day, the baby's condition was so poor that it was felt that intravenous feeding could no longer support the infant if the mass were not removed. Surgical excision was performed, without mishap, through a flank incision. Ether anesthesia was used through a vaporized unit. Some of the larger cysts were deflated in order to facilitate removal of the kidney.

Almost immediately after the operation the baby began to take fluids by mouth, no vomiting occurred, and the infant began to gain. He was discharged on June 10, 1954, the 13th postoperative day.

The excised kidney measured 7×4×4 cm. and consisted of multiple cysts measuring from 0.2 cm. to 3 cm. The ureter was rudimentary but patent.

Fig. 1*A* (Case 1).—Preoperative intravenous urogram showing normal function and morphology of right kidney and no function of left kidney.

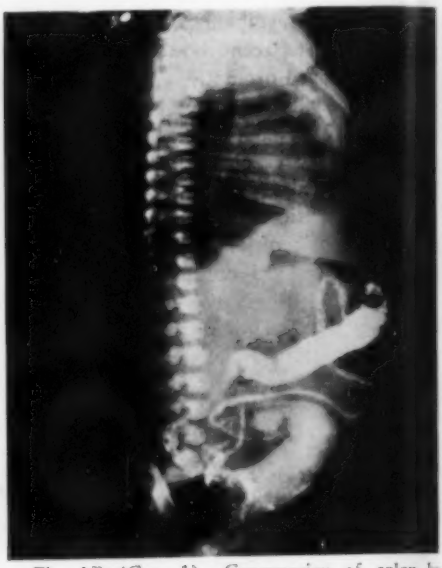

Fig. 1*B* (Case 1).—Compression of colon by large renal mass.

In March, 1955, the child was again admitted to the hospital for treatment of an upper respiratory infection. Urea N was 16, and a repeat intravenous urographic study showed normal right renal function and morphology.

Case 2.—A boy was born March 2, 1952. At the initial examination, bilateral undescended testes were noticed, but no mention was made of an abdominal mass. On the sixth postnatal day, the baby's stools were seen to be streaked with blood and two abdominal masses could be felt in the left side of the abdomen. When the plain film of the abdomen was viewed, a large mass which had a uniform ground-glass appearance was detected in the abdomen. After an injection of a renal visualizing dye, no dye was noticed in the left kidney but the right kidney was visualized (Fig. 2). The baby had persistent vomiting with an elevation of temperature to 101 F. His poor general condition did not allow any definitive surgical treatment; but, as the abdominal mass was getting larger and disturbing the adjacent bowel, aspiration of the mass was undertaken and 50 cc. of clear urine-like fluid was obtained. Following this treatment, the infant began to gain. Two and one-half months after birth, his condition was so improved that nephrectomy was possible. The specimen weighed 30 gm. and measured 8×6×3.5 cm. It was grossly cystic and composed of a conglomerate mass of numerous cysts ranging from 0.5 to 3.5 cm. The ureter showed no lumen at the ureteropelvic junction. Microscopic examination of the excised kidney showed many large groups of tubules that formed cysts (Fig. 3).

Case 3.—A white girl was born prematurely on Sept. 28, 1948, after normal pregnancy and delivery. The condition of the infant was good at birth. Initial physical examination revealed a multioculated mass occupying the entire left ab-

Fig. 2*A* (Case 2).—Plain film of abdomen showing large mass in left renal area.

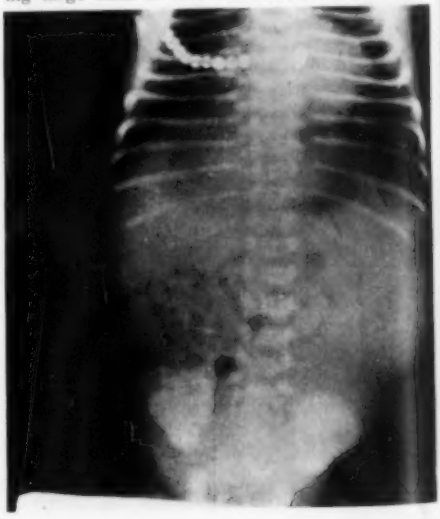

Fig. 2B (Case 2).—Intravenous urogram; normal right renal function and morphology—left side not visualized.

Fig. 2C (Case 2).—Lateral view, compression of transverse colon by left-side mass.

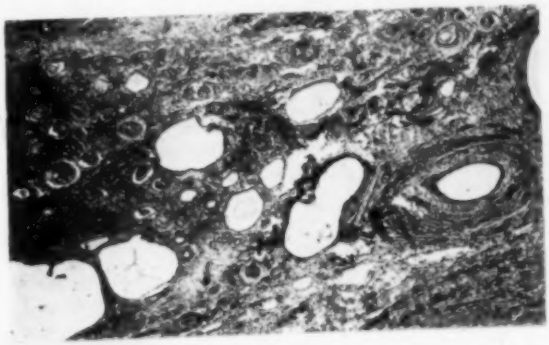

Fig. 3 (Case 2).—Microscopic appearance of renal cysts in the remaining parenchyma of excised kidney.

Fig. 4 (Case 3).—Gross specimen, resected unilateral multicystic kidney.

domen and extending into the pelvis. The mass was large enough to cause a noticeable bulge in the abdominal wall and was easily transilluminated. Laboratory examination, including complete blood count, urinalysis, and blood urea nitrogen, was essentially normal for a premature infant. Gastrointestinal and barium enema x-ray studies revealed a retroperitoneal mass displacing the abdominal contents to the right. Intravenous pyelogram showed normal kidney structures on the right side. The left calyceal structures could not be visualized.

Operative intervention was delayed because of the small size of the patient and her apparent good condition. The child progressed satisfactorily for about three weeks and then began to have difficulty in feeding and vomited frequently. On Oct. 29, 1948, a multicystic kidney was removed through a left flank incision (Fig. 4). The left ureter was noted to be obstructed and rudimentary. The organ was a kidney-shaped mass of clustered, cystic structures, thin walled and filled with straw-colored serous fluid. The over-all measurement of the mass was 8.5×5×6.5 cm. The encrusted cysts ranged in size from 1 to 2 cm., to a maximum of approximately 4 cm. These cysts were clustered about a central fibrous red and gray cord that only faintly resembled a ureter.

Microscopically, there was extreme dilatation and cyst formation of a number of nephron units. Some of the cysts contained distorted glomerular tufts. Among the various cystic structures were found nephron units which were normal.

The child's postoperative course was uneventful. One year later she was admitted for reevaluation. Growth and development were normal. Laboratory evidence of nitrogen retention was lacking and an intravenous pyelogram at that time showed a normal right kidney.

Summary

Three cases of unilateral multicystic kidney disease in the newborn with satisfactory surgical therapy are presented. Review of the current concepts of this disease are discussed.

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Carcinoma of the Thyroid in Children

A Report of Ten Cases

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In 1950 Duffy and Fitzgerald [1] reported a series of 28 children with thyroid carcinoma, of whom 9 had received irradiation to the thymic area in infancy. Hesitant to draw conclusions from these figures, Duffy and Fitzgerald did suggest that the possible relationship of thymic irradiation and thyroid carcinoma "might be profitably explored." Although neither the report of Horn and Ravdin [2] in 1951 nor that of Warren and co-workers [3] in 1953 presented comparable statistics regarding the association of irradiation in infancy and later development of thyroid carcinoma, other studies have appeared which indicate that it is well worth while to pursue this line of inquiry. Simpson and her colleagues [4] reported that of 1400 children who had received thymic irradiation in infancy 6 subsequently developed thyroid carcinoma and 9 thyroid adenoma. In a control series of 1795 untreated siblings of the irradiated children, there were no cases of thyroid cancer and only one of thyroid adenoma. Winship and Chase [5] reported in 1955 that of 116 of the patients in their collected series of cases of childhood carcinoma upon whom pertinent information was available, 16 were stated to have received irradiation in infancy. In a more recent report, dealing with an enlarged series, Winship [6] stated that irradiation to the thymus had been given in about 20% of his collected cases of childhood thyroid carcinoma from the United States. Striking figures were reported by Clark,[7] who stated that of 15 children with thyroid carcinoma coming to his attention all had "been subjected to prior irradiation to areas where the thyroid gland or portions of it could have been included in the field of irradiation."

Several reports by Winship * have served to call attention to the increased frequency of diagnosis of childhood thyroid cancer. Winship has collected and analyzed published cases of childhood thyroid carcinoma and has unearthed many previously unreported cases by means of a widely circulated questionnaire and personal canvass. In 1951 he reported that there had been nine cases of carcinoma of the thyroid in children under 15 years of age published in the world's literature from 1899 to 1930, thirty-four more from 1931 to 1940, and fifty additional cases from 1941 to 1950. The addition of 4 of his own plus 95 hitherto unpublished cases, enabled Winship to include a total of 192 cases in this report. By 1955, Winship and Chase had been able to collect 93 more cases to increase the series from 192 to 285. In a subsequent report in 1956, Winship stated that his collected series stood at 334 cases. These included 167 cases from the literature and 167 that were unpublished. In a large series of childhood thyroid carcinoma reported from the Mayo Clinic by Hayles and associates,[9] 21 of the total of 41 cases were diagnosed from 1909 to 1947 and 20 were seen from 1949 to 1954. In this paper no mention was made of previous irradiation.

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* References 8, 5, and 6.

Findings in Ten Cases of Thyroid Carcinoma in Children

Case No.	Sex	Age, Yr.		History of Previous Irradiation	Interval Between Radiation & Diagnosis	Presenting Finding	Thyroid Tumor		Metastases		Primary Size	Histologic Type	Vascular Invasion	Treatment	Survival Time	
		At Onset	At Diag.				Nodular	Diffuse	Cerv. Lym. N.	Other					From Onset	From Diagnosis
1	F	15	15	X-ray for cervical adenitis at 6 yr.	9 yr.	Right cervical lymph-node enlargement	–	–	+	Soft tissues of neck	?	Pap. & foll.	?	I^{131} followed by extensive rt. radical neck dissection	8 yr.	8 yr.
2	F	12	14	X-ray for cervical adenitis at 16 mo.	12 yr.	Thyroid and bilat. cervical lymph-node enlargement	+	–	+	Soft tissues of neck; left clavicle	..	Pap. & foll.	–	Partial rt. lobectomy; bilat. radical neck diss. (incomplete removal) x-ray; I^{131}	7 yr.	5 yr.
3	M	6	11	.....	..	Thyroid enlargement	+	–	+	Soft tissues of neck incl. larynx	4.0× 2.5× 1.8 cm.	Foll. & pap.	+	Partial ablation of thyroid; local excision cerv. Ln., bilat. (incompl. removal); x-ray	8 yr.	3 yr.
4	F	12	12	.....	..	Thyroid and bilat. cervical lymph-node enlargement	–	+	+	....	2.0× 1.5× 1.5 cm.	Pap. & foll.	–	Total ablation of thyroid; bilateral radical neck dissection	2½ yr.	2½ yr.
5	M	4	4	X-ray at 6 mo. for enlarged thymus	3 yr.	Bilateral cervical lymph-node enlargement	–	–	+	Pulmonary	3.5× 2.0× 1.5 cm.	Pap. & foll.	+	Total ablation of thyroid; bilateral radical neck dissection; I^{131}; desiccated thyroid	1½ yr.	1½ yr.
6	M	6	6	X-ray at 4 mo. for enlarged thymus	5 yr.	Thyroid and right cervical lymph node enlargement	+	–	+	....	1.8× 1.5× 1.2 cm.	Foll. & pap.	+	Subtotal thyroidectomy; bilateral radical neck dissection (incomplete removal); x-ray; I^{131}	1½ yr.	1½ yr.
7	M	8	8	X-ray at 4 mo. for enlarged tonsils	7 yr.	Thyroid and left cervical lymph-node enlargement	+	–	+	Pulmonary; soft tissues of neck incl. trachea	?	Foll. & pap.	+	Total ablation of thyroid; no neck dissection; x-ray; I^{131}; desiccated thyroid	2½ yr.	2½ yr.
8	F	6	7½	X-ray & radium at 5 mo. for hemangioma of left side of head, face, and upper lip	5 yr.	Thyroid enlargement	+	–	+	Pulmonary; soft tissues of neck	?	Foll. & pap.	+	Biopsy only surgical procedure; I^{131}	2 yr.	½ yr.
9	F	11	11	Radon seeds at 3½ mo. in hemangioma midway between left breast and shoulder	10 yr.	Thyroid enlargement	+	–	–	....	1.8 cm.	Foll. & pap.	+	Right lobectomy; x-ray	9 mo.	9 mo.
10	F	11	11	X-ray at 6-8 mo. for enlarged thymus	10 yr.	Thyroid and bilat. cervical lymph-node enlargement	+	–	+	Soft tissues of neck incl. trachea	3.0 cm.	Pap. & foll.	–	Excision L. lobe, isthmus & med. portion r. lobe; left rad. neck dissection (incomplete removal)	4 mo.	3 mo.

Interest in the two points brought out in the foregoing review of the literature led us to undertake a survey of all cases of thyroid carcinoma which have been admitted to Children's Hospital of Pittsburgh. Eight cases were found, to which we have added two cases seen in nearby hospitals. Analysis of these cases has yielded information bearing on the two problems under discussion, namely, that of the possible etiologic relationship of previous irradiation to thyroid carcinoma and also the problem of increased incidence of the disease.

Case Material

Sources.—At Children's Hospital of Pittsburgh there have been eight cases of thyroid carcinoma in children under 16 years of age. From 1926 through 1950 only one case was found, during a period when there were 88,392 admissions. In the five years from 1951 through 1955, seven additional cases of carcinoma of thyroid were encountered among 29,461 admissions. An attempt was made to find additional cases among hospital admissions by reviewing histologic material from all surgical operations known to involve thyroid from 1926 through 1955, with no result. It is of interest that there have been only four cases of benign nodular or adenomatous goiter operated upon in this hospital during the same period.

Two cases of thyroid carcinoma in children encountered in nearby general hospitals have been contributed† for the purposes of this study, to make a total of 10 cases herewith reported.

Details of these 10 cases are presented in the Table.

Clinical Findings.—Attention is called to several of the more important points contained in the Table.

Eight of the children had received irradiation some time before the appearance of thyroid carcinoma. In most cases this had been in infancy. In three of the patients the irradiation was for a presumably enlarged thymus. In two it was directed to hemangiomas, one of the face and one of upper chest. Two of the children received irradiation directed to enlarged lymph nodes. In one of these (Case 2) the mother stated that after two x-ray treatments an abscess of neck was incised and drained. In one child the irradiation had been given for enlarged tonsils. The period of time elapsing between the irradiation and the diagnosis of thyroid carcinoma varied from 3 to 12 years, with an average of 7.6 years. (In Clark's series of cases the elapsed period averaged 6.9 years.) In four of the cases the fact that irradiation had been given in infancy was discovered only by repeated questioning.

In 9 of the 10 cases there proved to be metastases to cervical lymph nodes. In six of these soft tissues of the neck were also invaded (Fig. 3). One presented tumorous involvement of the larynx, and in two the tumor was densely adherent to the trachea. Three of the children presented x-ray evidence of pulmonary metastases. In one patient there was x-ray evidence of a solitary metastasis to left clavicle. This girl was not one of those displaying pulmonary involvement.

† The records in Case 9 have been made available by Dr. H. G. Bregenser and Dr. J. G. Gruhn, while those of Case 10 were furnished by Dr. S. G. Hendry.

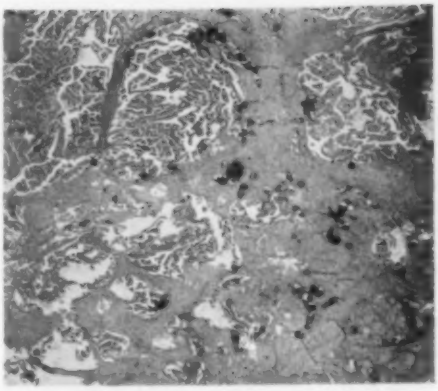
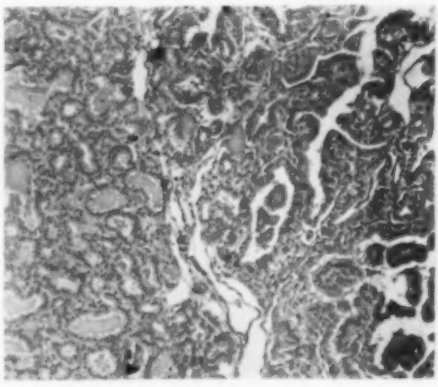


Fig. 1 (Case 4).—Photomicrograph × 11, showing primary tumor within the thyroid gland. In this field the tumor is nearly all papillary.

Fig. 2 (Case 1).—Photomicrograph × 140. A portion of a cervical lymph-node metastasis is seen, containing both papillary and follicular areas.



Pathologic Features.—The size of the primary tumor was known in six cases. The tumors varied in greatest diameter from 1.8 to 4 cm., averaging 2.6 cm.

The histologic classification as suggested by Winship was followed. No pure papillary tumors were included in this series of 10 cases, although none was without a papillary component. Great

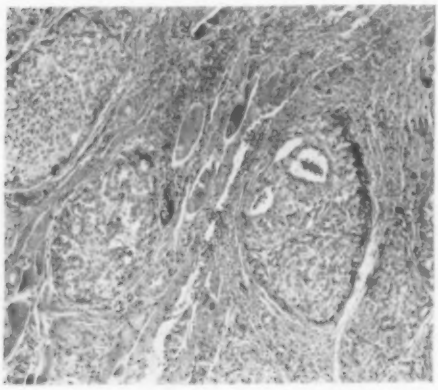
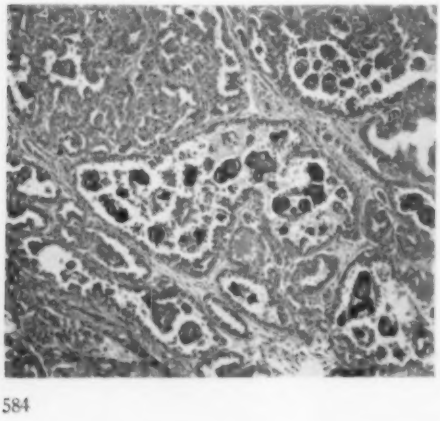


Fig. 3 (Case 3).—Photomicrograph × 140. Invasion of soft tissues (muscle) of neck by tumor which appears nearly solid in this section.

variability in histologic appearance was often presented in different areas of tumor in a given patient (Fig. 2). The greater the sampling available in each case with strong papillary tendencies, the more apparent it became that there was a considerable admixture of follicular areas. In the follicular portions of certain tumors there was great variability in the proportion of colloid-containing acini present.

Fig. 4 (Case 2).—Photomicrograph × 140. Many typical psammoma bodies are seen in papillary portion of cervical lymph-node metastasis.



In 9 of the 10 tumors, psammoma bodies were noted (Fig. 4). The possible diagnostic significance of such structures as an indication of malignancy in papillary lesions of the thyroid has been stressed by Crile and Fisher,[10] and Meissner.[11]

It was noted that the papillary processes in these tumors, either of primary or metastatic growths, presented well-formed densely fibrous stalks, not like the flimsy-appearing structure of benign papillary projections. This criterion of thyroid malignancy has been stressed by Fisher.‡

‡ Fisher, E. R., personal communication to the author.

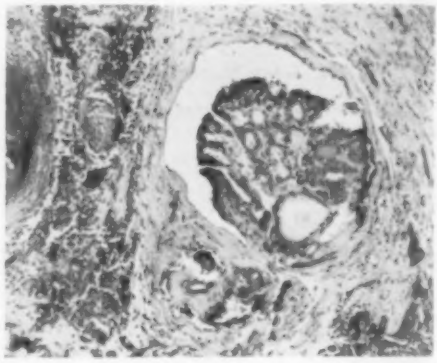


Fig. 5 (Case 5).—Photomicrograph × 140 of capsule of thyroid gland to show true invasion of endothelial-lined space by thyroid carcinoma.

Fig. 6 (Case 5).—X-ray of chest, showing extensive pulmonary metastases.

The histopathologic diagnosis was not difficult in these cases. In half the instances the first tissue submitted was of a metastatic lesion in lymph node. It is also true that during nearly all of the period in which these cases came to operation the suspicion index for juvenile carcinoma of thyroid has been very high.

Present Status.—All of the 10 patients are alive on the date this report was submitted. Therapy is summarized in the Table.

Of the patients without pulmonary metastases, two are believed to be free of disease (Cases 4 and 9). Five in which residual tumor remained after completion of surgical procedures are carrying on normal activities. All three children displaying pulmonary metastases by x-ray are in school. In none is there serious limitation of physical activity. In one of these patients there has been disappearance of lung lesions, judging by repeated x-ray examinations. This patient (Case 7) has received x-ray and I^{131}, as well as desiccated thyroid.[12] In the patient who presented x-ray evidence of a solitary metastasis to bone, the lesion was observed to undergo complete regression over an 18-month period, following I^{131} therapy.

Comment

Etiology and Incidence.—The problem posed by the frequent association of irradiation in infancy and juvenile thyroid carcinoma is a serious one. So far, a definite relationship has not been proved.

The clinical series reported by Duffy and Fitzgerald, by Clark and by us, represent groups of patients in which it may be assumed that a careful attempt was made to find out in each case whether or not there had been previous irradiation. If one assembles the cases from these three series, making allowance for our Case 1 (which also appears in Clark's series), one finds that of 52 children with thyroid carcinoma in 31, or 59.6%, there was a history of previous irradiation. This percentage is striking. It is possible that in the series reported by Ravdin and Horn and by Warren and associates more pointed questioning might have elicited information that there had been previous irradiation in a higher percentage of cases. We were impressed by the value of careful and even repeated questioning in our series, since it doubled the number known to have been previously irradiated.

Several points have been raised in opposition to the belief that irradiation in infancy may be a factor in the genesis of juvenile thyroid cancer. One is that in those cases wherein the irradiation was directed toward cervical adenitis, the lymph-node enlargement at time of therapy represented metastatic carcinoma rather than an inflammatory lesion.[6] This argument is not easily refuted, in view of the fact that in a few reported cases of childhood thyroid carcinoma the disease appeared to be present from birth. Another point which has been raised is that there may be a relationship between thymic disease and the development of thyroid carcinoma and that if thyroid carcinoma appeared after earlier irradiation to an "enlarged thymus," the tumor was related to the thymus or thymic disease and not the irradiation.§ We know of no evidence to support this. Lastly, the argument is advanced that when irradiation is applied to the thymus, tonsils, or most enlarged cervical lymph nodes the field of radiation does not include the thyroid.[13] Certainly the irradiation applied to the patients in the present series was not such as to necessarily include thyroid tissue in the field of irradiation. However, it was at least near the thyroid area in each instance.

Of the eight cases irradiated in our series, in only the two with hemangiomas can the indications for such therapy be considered strong.

A question that naturally arises in discussions of the possibly increasing incidence of juvenile thyroid carcinoma and reasons therefor is, if irradiation in infancy is a factor in the genesis of juvenile thyroid carcinoma, why have there not been more cases diagnosed in the past? Certainly the use of irradiation in the treatment of "enlarged thymus" and other benign conditions in infancy has been common in many sec-

§ Caulk, R. M., in Lattman, I., and others[18]; Reference 14.

tions of the United States since 1930 or earlier. Have many cases of thyroid carcinoma gone unrecognized in childhood and, because of the indolent nature of the disease, reached adult life before the late frankly malignant characteristics made diagnosis inescapable? This is a possibility.

There has been a great change in our awareness of the problem of juvenile thyroid carcinoma and in the application of diagnostic methods during the past decade. Winship has pointed out that the practice of removing enlarged cervical lymph nodes and thyroid nodules has been and is increasing.

As has been stated forcefully by Dennis,[14] more surveys of the type conducted by Simpson and co-workers are imperative in order to arrive at a solution of the problem presented by the frequent association of irradiation in infancy and childhood thyroid carcinoma.

Clinical Findings.—Thyroid nodules in children require prompt and thorough investigation. As has been stressed by others,‖ there is even more chance that a nodule in the thyroid of a child will prove malignant than a nodule in the thyroid of an adult. At Children's Hospital of Pittsburgh there have been four patients with benign thyroid nodules admitted since the hospital was occupied in 1926, during a period when eight carcinomas of thyroid have been observed.

Persistent firm enlargement of cervical lymph nodes in a child should make one suspect thyroid carcinoma. Enlargement of cervical lymph nodes only was the presenting symptom in 30% of the children in Winship's large series. This was true of 2 of 10 patients in our series.

The combination of thyroid and cervical lymph-node enlargement, dual presenting findings in 58% of Winship's series, was noted in 5 of our 10 patients. It is in these patients that clinical diagnosis is most accurate.

‖ References 2, 3, 8, and 6.

Therapy and Follow-Up.—The present series has been under observation for but a short time. Winship has stressed the need for long-term follow-up in series of juvenile thyroid carcinoma, because of the naturally slow progression of the disease. Evaluation of any form of therapy is difficult, since children with undiagnosed and untreated thyroid carcinoma may survive and continue normal activities for many years after appearance of cervical lymph-node metastases.

Summary

Ten cases of carcinoma of thyroid in children are reported from the Western Pennsylvania area, nine of which were diagnosed in the past six years. These figures would suggest that there has been an actual increase in the incidence of childhood thyroid carcinoma.

Eight of these ten patients had received irradiation to the face, neck, or chest area from 3 to 12 years before diagnosis of their thyroid carcinomas.

All of the patients are alive as this report is submitted, having survived for periods ranging from three months to eight years after diagnosis.

Nodular thyroid enlargement should not be taken lightly, especially in children. Such nodules should be widely excised and submitted for microscopic examination. Practicing physicians should also be aware of the possible significance of persistently enlarged cervical lymph nodes in children. In many instances of thyroid carcinoma this clinical finding precedes thyroid enlargement.

Follow-up studies of large series of children who have been irradiated in infancy are necessary in order to help arrive at a solution of the problem of the association of previous irradiation and thyroid carcinoma.

Until definite information is available as to whether or not previous irradiation plays a role in the genesis of thyroid carcinoma,

the use of ionizing radiations in the treatment of vague or non-neoplastic conditions in infancy should be reduced to a minimum.

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Determination of Low Percentages of Fetal Hemoglobin in Blood of Normal Children

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Until recently, fetal hemoglobin was a protein which could be detected in human blood only during the first year of life. Therefore the interest in this hemoglobin was mainly limited to those who were interested in infant physiology. Since Vecchio's discovery that fetal hemoglobin is found in large amounts in the blood of patients with Cooley's anemia, the interest of hemotologists has increased. It is now known that also in patients with sickle-cell-syndrome anemia (and perhaps in other hereditary hemolytic anemias) fetal hemoglobin may occur. An accurate method for the determination of small percentages of fetal hemoglobin is therefore important. The usual technique for the determination of abnormal hemoglobins is paper electrophoresis. Quantitatively the results are not very accurate. With this technique, moreover, the separation of adult and fetal hemoglobin is poor. Far better are the results obtained with the alkali denaturation method. The great differences in resistance to alkali between fetal and adult hemoglobin makes it possible to estimate the amount of fetal hemoglobin present in the mixture of the two. The method of Singer and coworkers,[1] as well as those of Künzer [2] and of Brinkman and Jonxis,[3] is based on this pecularity.

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The precipitation method of Singer and associates has the disadvantage that the results obtained for high concentrations of hemoglobin are found to be too low.[4] Moreover, it is doubtful that the alkali-resistant fraction that can be detected in the blood of many adults is composed mainly of fetal hemoglobin. The optical method of Brinkman and Jonxis has the disadvantage that low concentrations of fetal hemoglobin (under 10%) cannot be measured accurately. The reason is that in this method the increase of extinction caused by the formation of alkali hemochromogen is measured at a wavelength of 650 mμ. At this wavelength the extinction of hemochromogen is about 10 times as great as that of oxyhemoglobin. When small amounts of fetal hemoglobin are present, the extinction is so high after only a few minutes that the slight increase in the next 10 minutes caused by the denaturation of fetal hemoglobin can hardly be measured. Therefore it is preferable to measure the formation of the alkali hemochromogen at wavelength 576 mμ and not at 650 mμ. At 576 mμ the extinction of the oxyhemoglobin is about three times as great as that of the alkali hemochromogen. During the alkali denaturation there is not a rise, but a decline, in extinction. Therefore the method becomes more accurate for the determination of low percentages of fetal hemoglobin.

Betke has already mentioned the possibility of the use of wavelength 576 mμ.[5] This procedure has two disadvantages. The maximum in light absorption at 576 mμ is very sharp; it is therefore necessary to use an accurate spectrophotometer (Beckmann). The second disadvantage is that the dif-

ference in extinction between oxyhemoglobin and alkali hemochromogen is smaller at wavelength 576 mμ than at wavelength 650 mμ. In spite of these disadvantages we have tried to develop a method working at wavelength 576μ. Our procedure diverges only slightly from that described by Brinkman and Jonxis. Instead of 0.1 N NaOH, 0.06 N NaOH is used; 0.1 cc. of blood is diluted with 10 cc. of water to which 2 drops of NH_4OH 10% is added. The extinction of this solution is measured at wavelength 576 mμ (E_B). After that 0.1 cc. of the same blood is diluted with 10 cc. 0.06 N NaOH to which 2 drops of NH_4OH 10% is added. Each minute, especially between 5 and 15 minutes, the extinction is measured (E_T). Then the solution is placed in a water bath at 37 C for 15 minutes. After cooling to room temperature the extinction is measured again (E_E). The quotient $E_B:E_E$ should be constant. The concentration of the still undenaturated hemoglobin at a certain moment can be calculated:

$$\frac{E_T - E_E}{E_B - E_E} \times 100$$

Since the denaturation of the fetal hemoglobin behaves like a monomolecular reaction, the logarithm of the percentages of undenaturated hemoglobin at different moments plotted against time will form a straight line. By extrapolation to 0 time the percentage of fetal hemoglobin in the original blood can be calculated (Fig. 1). We have tested the accuracy of the method in the following way:

Hemoglobin samples obtained from cord blood with a known hemoglobin concentration and a high fetal hemoglobin content and from adult blood with the same total hemoglobin content were mixed. The hemoglobin was prepared and purified by the method described previously.[6] The fetal concentration in the cord blood was determined by the method of Brinkman and Jonxis. The adult blood contained 0.3% fetal hemoglobin.[7] This has been determined by means of a method on the principle of the difference in amino acid composition between fetal and later hemoglobin. Table 1 shows the results. It turns out that the found fetal hemoglobin percentages are in good agreement with the

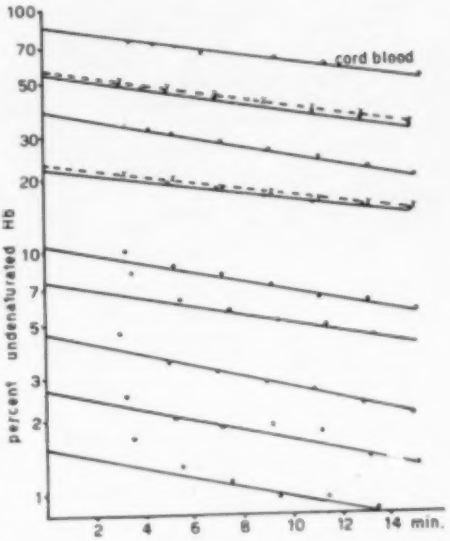

Fig. 1.—The solid line indicates the alkali denaturation curves of mixtures of adult and fetal hemoglobin at 576 mμ. The broken line indicates the same determinations at 650mμ (method of Brinkman and Jonxis).

TABLE 1.—*The Quantitative Estimation of Fetal Hemoglobin in Mixtures from Hb-A and Hb-F, by the Optical Alkali Denaturation Method at 576 Mμ and 650 Mμ**

		Estimated % F-Hb	
Sample	Calculated % F-Hb	650 Mμ	576 Mμ
1	58.2	56	55
2	44.2		38
3	46.6		44
4	33.4		31
5	22.6	23	22
6	20		20.5
7	18.2		17.5
8	11.4	9	10.5
9	10.3	10	9.8
10	7.3		7.5
11	5.6		4.5
12	3.8		4.4; 4.0; 4.7†
13	3.6		4.1
14	2.9		2.7; 2.6†
15	1.4		1.8; 1.5†
cord blood		85	85

* By the method of Brinkman and Jonxis[8]
† Duplicate estimations

TABLE 2.—*Quantitative Estimation of Fetal Hemoglobin in Mixtures of Hemoglobin A and F with the Optical Alkali Denaturation Method at Wavelength 576 Mμ and 650 Mμ for Low Fetal Hemoglobin Concentrations*

Sample	Calculated % F-Hb	Estimated % F-Hb	
		650 Mμ	576 Mμ
1	15	14.5	14
2	10.2	11.5	9.8
3	6.9	4.4	7.2
4	5.1	too inaccurate to get a value	4.2; 5.0; 5.1; 5.2; 6.2; 6.6; 6.6
5	4.1		4.4
6	3.1		4.3
7	2		3
8	1		1.8

The average for sample 4 is with the 576 wavelength method 5.56%; standard deviation 0.84.

amounts added in fact. Quantities of 1% can still be measured with some accuracy. For higher percentages there is also a good agreement with the results obtained by the Brinkman and Jonxis method, at 650 mμ.

Table 2 gives a comparison of the results obtained with both optical methods for mixtures with a low concentration of fetal hemoglobin. The mixtures were again made by mixing cord blood with adult blood which contained no appreciable amount of fetal hemoglobin. From one sample with a calculated percentage of fetal hemoglobin of 5.1%, seven determinations were made. For fetal hemoglobin concentrations lower than 6% no value of any accuracy could be obtained with the 650 mμ method.

We have used the described technique in order to study the disappearance of the fetal hemoglobin from the blood during the first years of life. Blood from a number of healthy full-term infants of different ages has been examined (Fig. 2). It proves that, as has been shown previously by various investigators,* at about 20 weeks after birth the percentage of fetal hemoglobin has dropped to about 5%. After that moment a small amount of fetal hemoglobin can still be demonstrated by our method for considerable time. In children older than 1½ years we could not detect it any longer. That means that the percentage has dropped below the 1% level. The immunological investigations of Chernoff [11] and also our own work [7] show that in later life minute amounts of fetal hemoglobin (less than 0.5%) are still present in the blood.

Summary

Description of an optical method for the determination of low percentages of fetal hemoglobin is presented. In the blood of normal children the fetal hemoglobin percentage decreases after birth till at the age of 20 weeks a percentage of about 5% has been reached. After the age of 18 months the percentage falls below 1% and can no longer be demonstrated with this method.

* References 3, 5, 8, 9, and 10.

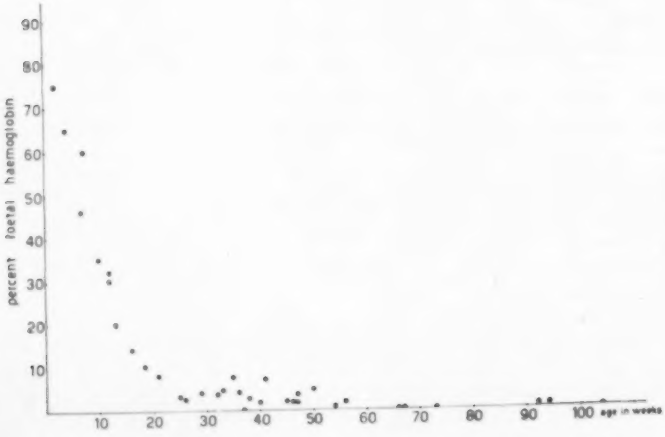

Fig. 2.—The disappearance of fetal hemoglobin in the blood from healthy full-term infants during the first years of life, especially after 20 weeks.

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Struma Lymphomatosa (Hashimoto's Disease)

Report of a Case in Thirteen-Year-Old Boy

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Struma lymphomatosa is characterized as a progressive disease of the thyroid gland of unknown etiology, occurring almost entirely in females. It appears predominantly in middle age. Although there is a divergence of opinion as to whether it is inflamatory in nature, it is generally classified as a form of thyroiditis. The thyroid gland is grossly enlarged, firm, rubbery, and may be lobulated with a scalloped border. The capsule of the gland is intact with no adhesions to underlying or adjacent structures. Both lobes of the gland are involved in almost all cases. Microscopically, there is marked lymphoid infiltration, atrophic follicles with scanty colloid present, and mild fibrosis. Frequently, there are large hyperplastic lymph nodules with germinal centers present.

The patient commonly complains of fullness of the neck and dysphagia. The results of thyroid function tests are variable, and there seems to be no specific diagnostic pattern. Gribetz and co-workers [12] found the PBI values to be elevated in three of five young girls with this disease who manifested no signs or symptoms of thyrotoxicosis. The BEI in two of these cases was normal. The I^{131} may be elevated and the B.M.R. may be low. However, the value of any thyroid function test should be evaluated in the light of the possibility of previously administered thyroid medications. There have been instances of clinically mild hypothyroidism.

Surgical intervention is employed because of the inability to exclude carcinoma by any other means; secondly, to relieve symptoms of pressure; and, thirdly, to accomplish a cosmetic effect when the goiter is large. With an increased recognition of this entity in children, needle biopsy of the thyroid gland may be substituted for surgical exploration. The results of irradiation therapy are equivocal. Corticotropin (ACTH) and cortisone may relieve the symptoms but produce little or no change in the thyroid enlargement.

In three cases, all girls, large doses of thyroid were administered with a resulting shrinkage of the thyroid gland in two of them. Postoperative hypothyroidism occurs in about 70% of the cases.[8]

Struma lymphomatosa was first described in 1912 by Hashimoto.[1] Since then, there have been many additional case reports of this entity in the literature, by Graham in 1931,[2] McClintock and Wright in 1937,[3] Joll in 1939,[4] Statland and associates in 1951,[5] Lindsay and co-workers in 1952,[6] Furr and Crile in 1954,[7] Gribetz and associates in 1954,[12] Marshall and Meissner in 1955,[8] and Davis and Hanske in 1955.[13] An excellent review of the clinical and pathological aspects of this disorder was reported by Hazard.[9] In approximately 98%-100% of the various clinical series, the disease occurred in women. In fact, Blake and Sturgeon [10] found only 9 isolated cases in men prior to 1953. Marshall and Meissner [8] described two additional cases in men.

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The disease is relatively uncommon under the age of 20. Statland and co-workers [5] reviewed 51 cases, all of whom were females, and found that two cases occurred at the age of 10 and one at the age of 15 years. Gribetz, Talbot, and Crawford [12] found a total of 11 cases in children and added three reports in preadolescent and three in adolescent children—again, all females. Davis and Hanske [13] reported an 11-year-old girl with this disease. To our knowledge, the case described below is the only one reported in which struma lymphomatosa occurred in an adolescent or preadolescent boy. Although the diagnosis was made at the age of 13, it apparently had its inception when the child was 5.

Report of a Case

A 13-year-old white boy was admitted to the Long Island College Hospital with a complaint of swelling of the neck of 8 years' duration. The swelling was first noted by a friend of the family when the patient was 5 years old. This swelling had slowly increased in size and became more noticeable. He said he had experienced a feeling of a "lump in the throat as long as I can remember." There was an increase in the dysphagia during the six months prior to admission. There were no symptoms suggestive of thyrotoxicosis or myxedema. The patient was born and raised in New York City and had lived there all his life. He had always been in good health except for measles and a tonsillectomy at the age of 7 years.

Physical examination revealed a well-nourished but somewhat underdeveloped boy who appeared younger than his stated age. He was cooperative, alert, and responded intelligently to questions. There was absent pubic and axillary hair. The skin was warm but not moist. There was no exophthalmus or lid lag. Examination of the neck revealed a diffusely enlarged thyroid gland. The isthmus and both lobes of the thyroid were firm, with a nodular consistency. A 2-cm. nodule was palpated in each lobe and a ½-cm. nodule was present on the inferior border of the isthmus. The remainder of the thyroid was finely nodular with a lobulated border. There was a musical inspiratory wheeze heard throughout the chest but louder over the trachea. The heart, abdomen, genitalia, and extremities were normal.

Laboratory Examinations.—Blood hemoglobin, 13.1 gm/100 cc.; red blood cells, 4,450,000; white blood cells, 7450, with polymorphonuclears 54%; lymphocytes, 42%; monocytes, 3%; eosinophiles, 1%. Erythrocyte sedimentation rate, 5 mm/hour (Westergren). Hematocrit 38%.

Chemical Tests.—Fasting blood sugar, 78 mg/100 cc.; urea nitrogen, 14.1 mg/100 cc.; total cholesterol, 212 mg/100 cc.; cholesterol esters, 125 mg/100 cc.

Urinalysis.—Specific gravity, 1.006; color, amber; turbidity, clear; albumin, 0; sugar, 0; acetone, 0; microscopic, no casts or cells; 17-ketosteroids, 4.9 mg/24 hours.

Radioactive iodine uptake, 28.1%.

An electrocardiogram was normal.

A roentgenogram of the chest showed a soft tissue swelling of the neck. The heart and lungs were within normal limits. An esophagram showed moderate enlargement of the thyroid gland with no evidence of extrinsic pressure on the esophagus.

Roentgenograms of the wrists revealed the bone age compatible with physiological age.

Roentgenograms of the skull disclosed a normal sella turcica.

On the 11th hospital day, a subthyroidectomy was performed. The postoperative course was uneventful, and the patient was discharged, asymptomatic, one week later.

The surgical specimen consisted of two irregularly ovid and somewhat flattened pieces of tissue labelled "Thyroid—Right and Left Lobes." The larger piece measured 4×4×1.6 cm. in largest dimensions. On one cut surface there was a fibrous capsule of varying thickness. The cut surfaces presented an irregular lobular pattern and a tan color. The smaller lobules measuring between 0.2 and 1.2 cm. in largest dimensions bulged from the interlobular zone. Beneath the fibrous capsule there was a 1 cm. soft nodule, the cut section of which exhibited the characteristics of lymphoid tissue.

The second specimen measured 3.6×3×1.6 cm. in largest dimensions. On one surface there was a fibrous capsule of varying thickness. The other surfaces as well as the cut section revealed a lobular pattern similar to the specimen described above. In both specimens the cut sections presented a rather pale tan color.

Microscopically, multiple representative sections of the thyroid, from both lobes presented an essentially similar pattern. A few acini of small to moderate size contained colloid. The majority of the acini were of a small type and contained little or no colloid (Figs. A, C). The lining cells were cuboidal with a pale cytoplasm and relatively large nuclei with fine, even nuclear chromatin. The most impressive feature was a very extensive lymphoid infiltrate (Fig. B), both inter- and intralobular in its distribution. Germinal centers were numerous and large. In most places lymphoid tissue presented the dominant elements with adjacent thyroid inconspicuous and atrophic in its appearance. Connective

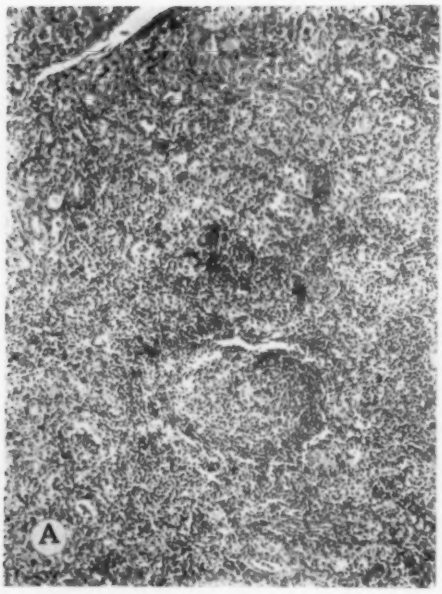
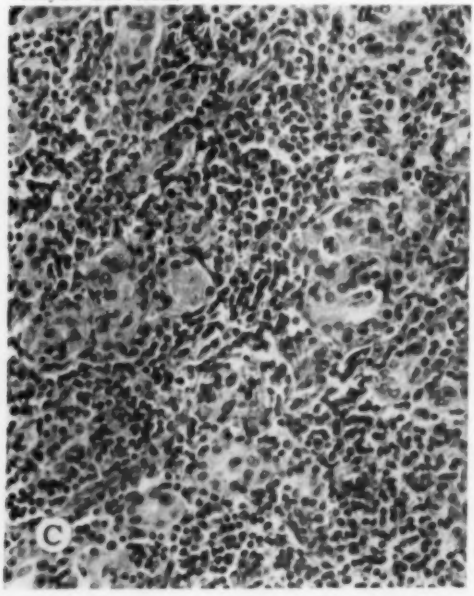


Fig. A.—Low-power view showing advanced follicular atrophy with replacement by lymphoid tissue. A lymphoid follicle is present. Right lobe mag. × 70. Hematoxylin and eosin.

Fig. B.—There is almost complete replacement of thyroid follicles by lymphoid tissue. Minimal interstitial fibrosis is present. Left lobe mag. × 70. Hematoxylin and eosin.

Fig. C.—A high-power area showing reduced number of small atypical follicles. There are multitudes of lymphocytes and fewer plasma cells between the deranged follicles. Mag. × 300. Hematoxylin and eosin.



tissue was evenly distributed and not significantly increased.

The diagnosis was Hashimoto's disease of the thyroid gland.

Summary

Herein is presented an unusual case of Hashimoto's disease, occurring in a 13-year-old boy. Previous reports and reviews refer almost exclusively to middle-aged women except for isolated instances in girls and men. A short résumé of the clinical and pathological features is discussed.

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Pharyngoconjunctival Fever

Report of an Epidemic Outbreak

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This article is a report on an outbreak of pharyngoconjunctival fever due to APC Type III virus which occurred in a children's camp during the summer of 1955. The adenopharyngeal conjunctival or APC group of viruses was isolated in 1952 by Huebner, Rowe, Bell, and others.* They studied surgically removed tonsils and adnoids by tissue culture technique. Through repeated subculturing of these tissues, they were able to unmask a new group of viruses. Because of the characteristic tissue culture degenerating effects produced by these micro-organisms, they were originally named "adenoid-degenerating agents". This was later renamed "adenoidal-pharyngeal-conjunctival viruses" or "APC viruses." As a result of the work first done in the U. S., investigation has been undertaken along similar lines in other countries. Zaiman and co-workers,[5] in England, have also been able to isolate this new group of viruses from surgically removed tonsils and adenoids and have noted the presence of antibodies in the majority of the adult population.

The APC group of viruses are at the present writing divided into 10 immunological strains. The various strains possess a common complement antibody but are separated by neutralizing antibodies which are specific for each strain.† Type 1, 2, 5, and 6 have been isolated from surgically removed tonsils and adenoids. Their clinical pictures are not clearly known but are believed to be responsible for many of the common nonbacterial upper respiratory infections found especially in children. Type 3 has been isolated from the conjunctivae, throat, and stool of patients with pharyngoconjunctival fever. Type 4 is identical with Hilleman's and Werner's RI-67 virus and has been found to be responsible for an epidemic outbreak of an upper respiratory disease in military recruits.‡ Type 7 has been found responsible for a similar type of upper respiratory infection in another group of military personnel.[10] Type 8 has been associated with epidemic keratoconjunctivitis.[11]

The clinical picture of pharyngoconjunctival fever or APC fever is characterized by conjunctivitis which is frequently unilateral in onset, pharyngitis, cervical adenitis, spiking fever of four-five days duration; the disease primarily affects children, and is usually epidemic in nature. The earliest known report in the literature of pharyngoconjunctival fever was in 1943. Derrick, in Australia, reported on three cases which he termed "swimming bath conjunctivitis."[12] In the summer of 1951, Cockburn studied an unusual epidemic in Greeley, Colo., which became known as "Greeley's disease.[13] Serological studies by Huebner performed at a later date revealed this epidemic to be due to APC Type III virus. In February, 1954, Parrott, Rowe, Huebner and associates[14] described eight cases of pharyngoconjunctival fever in one hospital. The diagnosis was established through the isolation of the virus and neutralization studies from acute and convalescent bloods. During the sum-

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* References 1-4.

† References 6 and 7.

‡ References 8 and 9.

mer of 1954, an epidemic of pharyngoconjunctival fever broke out in a children's day camp in Virginia and two neighboring residential communities. An excellent clinical and laboratory *arbeit* was accomplished by Bell, Rowe, Huebner and co-workers.[15] A total of 300 cases were seen. APC virus Type III was recovered in 80 patients. Specific antibody response was noted in the convalescent period. A recent epidemic of pharyngoconjunctival fever was reported by Wallis,[16] occurring March, 1955, in Carlisle, England. Viral studies are being investigated at the present time.

As can be seen from the summary of the literature on pharyngoconjunctival fever, there is a relative paucity of information on this subject. A recent epidemic in a large children's summer camp furnished us with additional clinical material which will be presented in the following paragraphs.

Description of Study

This study was made at a privately owned and operated boys' summer camp located in the central part of New Hampshire. These observations cover the period of camp operation from June 30, 1955, to Aug. 25, 1955. This camp is one of the oldest and most reputable camps in the state. It is a "sleep-away camp" as contrasted to a "day camp." In the latter the children devote a limited number of hours during the day to camp activities but return to their homes every night. In the "sleep-away camp" the children live at camp for eight weeks and return home at the end of the two-month period. There are no new campers added during the summer. The camp is divided into two separate geographic units—a junior mainland camp for boys from 5 to 12 years and senior island camp for boys from 12 to 16. The island camp is separated from the mainland camp by ¼ mile of water. The two camps operate as separate units. Their contact consists of occasional visits. Otherwise all sports, dining, and sleeping are carried out independently. The two camps use the same lake for swimming but in different areas. This is a fresh water lake, 31 miles long, and has 221 miles of shore line. The lake water at both camps is tested by the State Board of Health every summer. This sampling has revealed no bacterial contamination during the 25 years the camp has been in existence. There are no swimming pools.

The junior mainland camp has 150 boys ranging in age from 6 to 12; 15 waiters, ranging from 16 to 18 years; 30 mature male counsellors, and 15 kitchen personnel. There are a total number of 28 cabins which house the children. The bunks are 15 feet apart and are situated in a semicircle on the edge of the lake. They are divided into a junior row of cabins (bunks 1-14J, ages 6-10) and a senior row (bunks 14S-24, ages 10-12). The senior row is separated from the junior row of bunks by approximately 250 yards. The pioneer house which accommodates the youngest 15 boys in camp is situated about ⅛ of a mile from the other cabins. Each cabin, with the exception of the pioneer house, accommodates from three to six children and one to two counsellors. The cabins are equipped with hot and cold running water and toilet facilities. The sewage disposal is by septic tank. The water supply is chlorinated lake water, which is checked twice a summer by the State Health Department. The reports have always been satisfactory.

The senior island camp has 100 boys ranging from 12 to 16 years of age, 15 male counsellors, and 10 kitchen staff workers. There are 10 cabins situated on the lake front. The cabins are 20 feet apart and accommodate 10 boys and two counsellors. The bunks have hot and cold running water, and have toilet facilities shared by two adjoining bunks. The sewage disposal is by septic tank. The water supply is chlorinated lake water which has always been approved by the State Board of Health.

The mainland camp infirmary is a new building situated apart from regular camp grounds. It has nine large rooms which can accommodate about 20 children. There are

three lavatories and a completely equipped kitchen which is kept independent from the main camp kitchen. There is a second infirmary on the island camp. The medical department for both camps consists of two physicians and three nurses. There are medical office hours after each meal. It is routine to check temperatures of children reporting to sick call. The finding of temperature over 100 F is sufficient indication for admitting the child to the infirmary for observation. The camper is dismissed from the infirmary only after 24 hours of normal temperature. Through such a medical program, it is often possible to pick up illness at its earliest stages. One of us has been acting as camp physician for this camp for the past 15 years. With the exception of four years, there has been approximately 8% to 20% of the camp population admitted to the infirmary on the mainland camp every summer. On the island camp, where the campers are older, the infirmary admission rate has been lower, approximately 3% to 7% for the entire summer. There were four summers when exceptions to these usual percentages occurred. Larger numbers were admitted to the infirmary because of the following epidemics: measles in 1943, pleurodynia in 1948, poliomyelitis in 1949, and herpangina in 1952.

Description of Epidemic

A. *Mainland Camp.*—The mainland camp infirmary census from the start of the summer camp period on June 30, 1955, to the closing date on Aug. 25, 1955, is charted on Figure 1. Two distinct waves can be seen on this graph. The initial wave in which the illness was characterized by a very mild pharyngitis extended over a four-week period from July 1st to July 28th, reaching its height on July 19th. During this first wave of mild pharyngitis, 36% of the campers, 13% of the counsellors, no waiters, and no kitchen staff were affected. On July 19th, at the height of this period, 8% of the campers and 3% of the counsellors were in the infirmary.

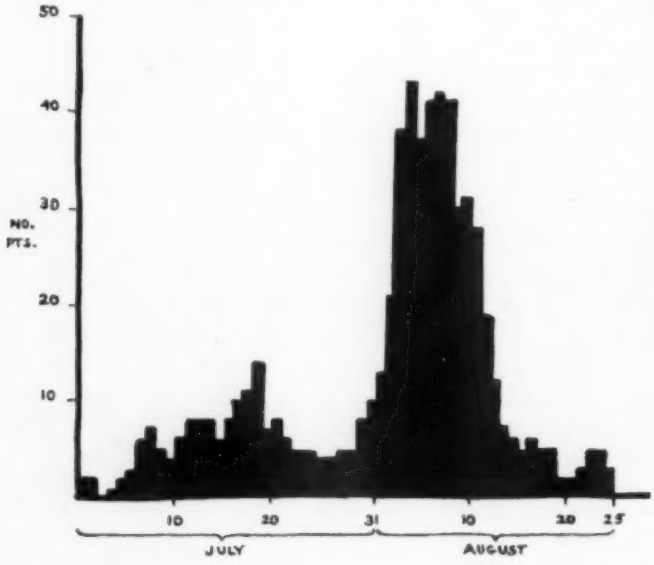

Fig. 1.—Infirmary Census of APC Fever, mainland camp, summer, 1955. Total number of campers, 150.

The second wave was explosive in nature and was characterized clinically by the more typical features of pharyngoconjunctival fever. This wave was a much larger and higher wave extending over a 4 week period from July 28th, 1955, to Aug. 25, 1955, and reaching its peak between Aug. 4th and 8th.

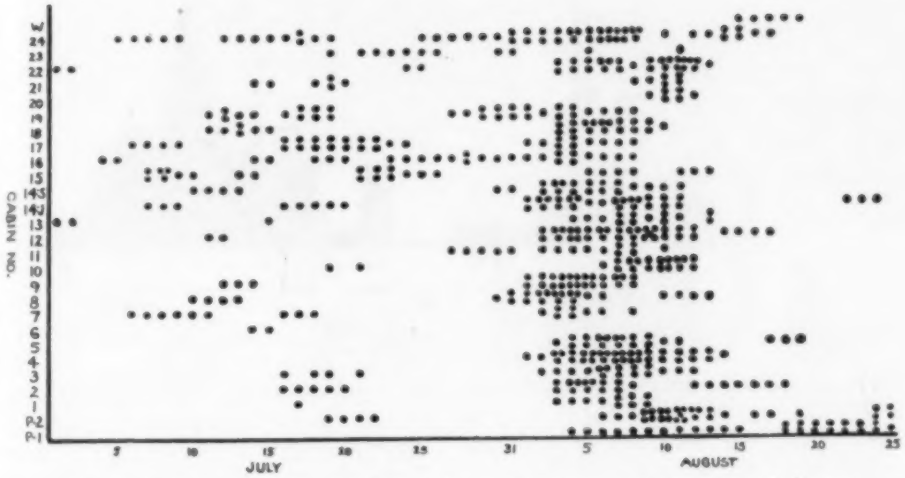

Fig. 2.—Incidence and cabin distribution of new admissions of APC Fever to infirmary, summer, 1955 (mainland camp).

There were 62% of the campers, 10% of the counsellors, 7% of the waiters, and no kitchen staff affected during the second wave. At the height of the second period on Aug. 4th, 25% of the campers and 7% of the counsellors were in the infirmary.

The cabin distribution of the patients affected by pharyngoconjunctival fever is seen on Figure 2. During the first smaller wave, one and rarely two campers from 20 out of the 28 cabins were admitted to the infirmary. There was a slightly higher incidence from senior row (bunks 14S-24, ages 10-12) than from junior row (bunks 1-14J, ages 6-10). The pioneer house which housed the youngest group in camp and which was situated slightly apart from the other bunks was not involved. During the second explosive wave, one, several, or all of the campers from all the cabins except one were affected. There was a slightly greater incidence of illness among the youngest children (bunks 1-14J and Pioneer House).

Figure 3 represents the number of new daily admissions to the mainland camp infirmary during the course of the summer. There were new admissions every day with the exception of 11 irregularly scattered days throughout the 2-month summer period.

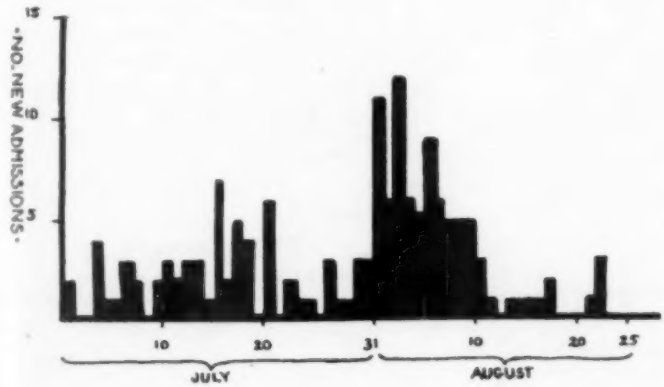

Fig. 3.—New admissions of cases of APC fever to infirmary, summer, 1955 (mainland camp).

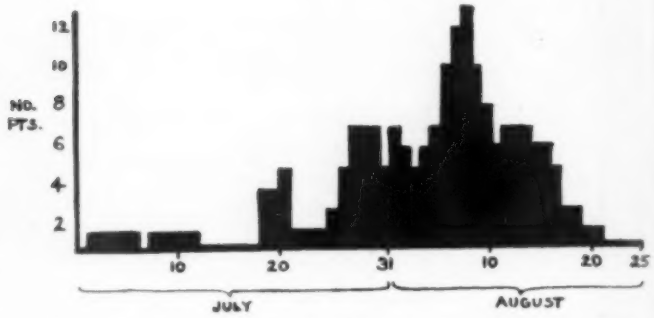

Fig. 4.—Infirmary Census of APC fever, island camp, summer, 1955. Total number of campers, 100.

The greatest concentration of new admissions occurred in the first 11 days in August, coinciding with the second epidemic wave. The pattern of the new admissions was not characteristic of a water borne or food borne epidemic in which there is a sudden massive explosive outbreak but rather typical of a respiratory spread infection.

B. *Island Camp.*—The island camp infirmary census is seen on Figure 4. The first smaller epidemic wave seen on the mainland graph (Fig. 1) is not clearly seen here. There was a slight rise in incidence of illness from July 19th to July 21st which coincided with the peak of the first wave found on the mainland camp. There were 14% of the island boys (ages 12-16), 6% of the counsellors, and no kitchen staff affected from June 30, 1955, to July 28, 1955. This first illness, as in the mainland camp, was characterized by a very mild pharyngitis. A second larger wave of illness, as seen on the mainland camp graph (Fig. 1), extended from July 28, 1955, to Aug. 21, 1955. It covered the same period of time; however, fewer campers were involved. There were 24% of the campers, 10% of the kitchen staff, and no counsellors affected during this period. At the height of the second wave on Aug. 7, 1955, eleven per cent of the campers were in the infirmary. The incidence of illness according to bunk distribution is charted on Figure 5. During the first wave only one or two campers from 4 out of 10 bunks were affected. During the second wave the infirmary had from every bunk one, occasionally two, and rarely three campers.

Figure 6 represents the daily admission rate to the island infirmary. There were only two admissions to the infirmary during the first two and a half weeks of the camp season. From July 19th through August 25th, there were new admissions to the

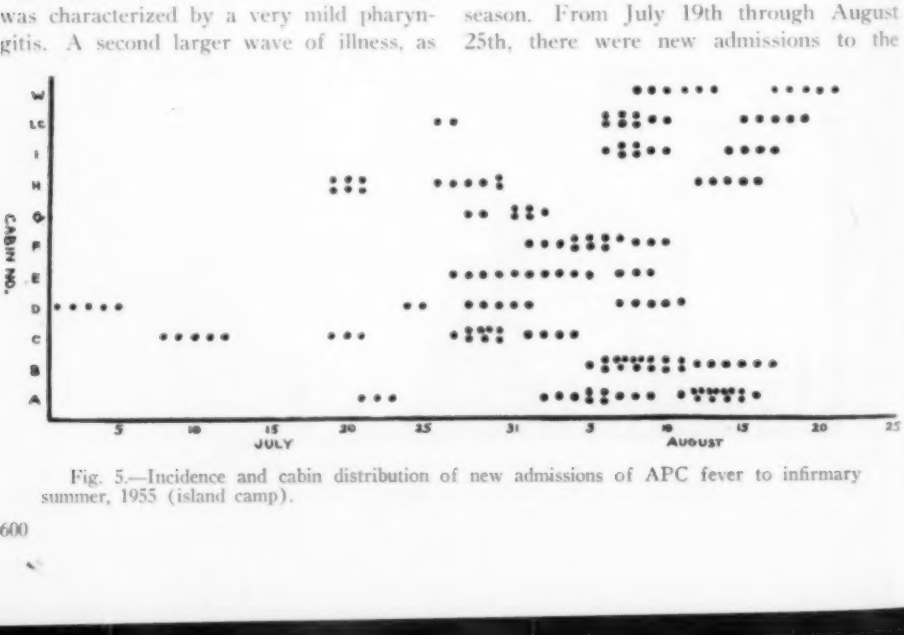

Fig. 5.—Incidence and cabin distribution of new admissions of APC fever to infirmary summer, 1955 (island camp).

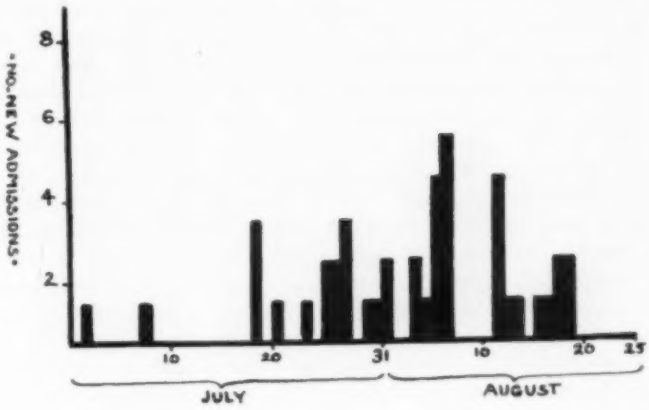

Fig. 6.—New admissions of cases of APC fever to infirmary, summer, 1955 (island camp).

infirmary on 50% of the remaining days of the camp season.

Clinical Description of the Disease

A. *Precipidemic Period.—First Wave, June 30-July 28, 1955.*—The clinical picture during the first wave of illness in July was that of a very mild pharyngitis. The complaints were minor and the findings very few. Most of the children complained of mild sore throat but otherwise felt fairly well. Physical examination revealed in some cases a fine pinpoint follicular hypertrophy of the anterior pillars of the tonsils. The pillars were occasionally slightly dusky in appearance. The tonsils were usually not injected or swollen. Frequently no physical findings could be found to account for the low-grade temperature elevation. The children remained in the infirmary for two to three days, the usual time being two days. Slight temperature was present for about 24 hours ranging between 100 F and 101 F. Campers were discharged on the second or third day after 24 hours of normal temperature. They were given no medication other than bed rest. They felt well during their infirmary stay. After discharge they were kept inactive for an additional 24 hours before resuming camp activities. The convalescence was uneventful.

It is routine to check the temperature of ambulatory campers who present themselves at the doctor's office if they complain of any respiratory symptoms, regardless of how minor they may be. Had it not been for this finding of a slightly elevated temperature on such routine examinations, many of the campers would not have been admitted to the infirmary during this first wave, since their complaints were so mild.

The conjunctivitis which was seen so typically during the second epidemic wave was an infrequent finding during the first period. The clinical entity of pharyngoconjunctival fever was not recognized at this time. The diagnosis of APC fever was not established until several days after the onset of the second wave. We did not know what type of upper respiratory infection we were dealing with during the early weeks of the summer. We did anticipate a larger outbreak toward the end of the first wave. The camp infirmary census at the end of the third week was far above the average total summer's illness for past seasons. We were at a loss to know what the nature of the infection could be. Our main concern was whether the first wave represented poliomyelitis, which was epidemic in nearby Boston. For want of a better term, we diagnosed the upper respiratory infection during the first wave as "herpangina-like syndrome."

B. *Epidemic Period—Second Wave, July 29-Aug. 25, 1955.*—The epidemic pe-

riod lasted for four weeks, from July 29, 1955, through Aug. 25, 1955. The epidemic on the mainland assumed the pattern of a high, narrow wave with a steep ascent and descent. During this period, 62% of the campers were affected.

The clinical picture was different from the first wave of illness, which occurred from June 30th through July 28th. The campers were sicker, the complaints were more numerous and of greater intensity, the course in the infirmary was longer, and the convalescence was often prolonged. We were not able to diagnose the illness from clinical means until the main epidemic was under way for several days. This camp is situated 130 miles north of Boston. Boston was in the midst of one of the worst poliomyelitis epidemics in its history. Our big concern at camp was whether this first minor epidemic wave of pharyngitis represented abortive poliomyelitis. It was not until the second wave was well under way, did we recognize the clinical picture as due to APC III virus. Our preoccupation with polio probably delayed our diagnosis of pharyngoconjunctival fever by several days.

The clinical features of the illness seen during the second epidemic wave will be given in greater detail in the following paragraphs.

1. Complaints: The major complaints were sore throat, headache, malaise, eye discomfort, and to a lesser degree abdominal symptoms, i. e., nausea, vomiting, abdominal discomfort. Other infrequent complaints were moderate stiffness and pain of the neck, back, and leg muscles. Various combinations of these complaints were present.

2. Physical Appearance: Most of the campers appeared sicker than during the first wave of illness. Many were toxic and lethargic and this persisted from one to three days after admission to the infirmary. This was so marked in a few of the children that suggestive diagnosis of encephalitis and poliomyelitis were entertained before we realized that the epidemic was due to the APC III virus. A smaller number of the campers had minimal complaints and physical findings but were admitted to the infirmary because of the presence only of low-grade temperature. These latter patients were similar to the mild cases seen during the first wave of illness.

3. Eyes: The pathology found in the eyes was limited to the conjunctiva. The conjunctival findings were present in about 80% and absent in 20% of the patients. Conjunctival findings were present with and occasionally without apparent constitutional involvement. There was no severe pain and no photophobia. The patients complained of slight irritation and occasionally slight itching. The conjunctival findings were characterized by granularity of the palpebral conjunctival and injection of the palpebral and bulbar conjunctiva. Granularity varied from a fine, almost microscopic peppering to a coarse, granular, cobblestone-like appearance. The injection varied from minimal to marked dilation of the blood vessels. In several cases hemorrhages of varying sizes and degree were seen on the ocular conjunctiva. There was little or no ocular discharge and little or no edema. No false membrane formation occurred. Superimposed secondary infection occurred in only one patient. Either monocular or binocular involvement occurred. There was usually a difference in the degree of ocular involvement noted in the two eyes. Frequently one eye cleared as the second eye became involved. Conjunctival involvement occurred at varying times in relation to the onset of generalized systemic manifestations, i. e., one to two days before, simultaneously, or after admission to the infirmary. In a few cases there was recurrence of eye symptoms after the patient was discharged from the infirmary. The usual period of eye involvement lasted from a few days to about two weeks. There appeared to be no after-effects except for slight follicular hypertrophy of the palpebral conjunctiva. No slit-lamp examination was employed although no corneal opacities were seen on ordinary examination.

4. Nose: The patient was usually admitted to the infirmary with slight or no nasal obstruction; however, during the course of the disease the nasal passages usually became very clogged. This was due to hypertrophy of the posterior nasopharyngeal lymphoid tissue and adenoids, and to a lesser degree due to swelling of the nasal turbinates. The marked nasal clogging was a great annoyance to many patients during the course of the illness. There was little or no relief from the ordinary nasal decongestants. Postnasal discharge was a common complaint after the patient was admitted to the infirmary. A heavy mucopurulent posterior nasal discharge was noted in most patients during the course of the illness. No severe acute sinusitis was seen, although the posterior nasal discharge frequently persisted for many days.

5. Tongue: The tongue varied from normal to strawberry-like in appearance. There was slight, moderate, or marked hypertrophy of the papillae which usually became increasingly prominent as the illness progressed.

6. Soft Palate: The soft palate was usually normal in appearance but occasionally showed a few pinpoint hypertrophied follicles. These were seen more characteristically on the anterior pillars of the tonsils. In a few cases the surface capillaries were injected and a few petechiae were seen. Several herpetiform lesions were noted in three patients.

7. Tonsils: The anterior pillars of the tonsils were involved in 80% of the patients. The characteristic picture seen was a few or many follicles varying from pinpoint to coarse granules in size scattered over the surface of the anterior pillars. Occasionally there was marked hypertrophy of two lymphoid nodules located on either side of the uvula. The color of anterior pillars was either normal or dusky in appearance.

The tonsils were either normal, slightly, or moderately injected. A few patients showed a more intense redness of the tonsils and pharynx; however at this period hemolytic Streptococcus was found in most of the throat cultures. Prophylactic sulfisoxazole (Gantrisin) was given to everyone for three days with eradication of the hemolytic streptococci. However, chemotherapy had no effect on the epidemic. Occasionally, well-encapsulated whitish glairy material was noted in the crypts of the tonsils and in the center of the enlarged posterior pharyngeal lymphoid nodules. In addition there was occasionally seen small irregular patches of whitish granular exudate on the surface of the tonsils.

8. Posterior Pharynx: The posterior pharynx was either normal in appearance or showed a moderate to marked hypertrophy of the lymphoid tissue. At times there was noted in the center of these lymphoid nodules similar whitish glairy encapsulated material described in the crypts of the tonsils. When the adenoids were present, there was marked hypertrophy which caused marked nasal clogging. Mucopurulent posterior nasal discharge was a common finding after the second day of the illness.

9. Ears: The external auditory canals and drums were involved in one-third of the patients. This consisted of injections of the canal and the drum. The drums did not bulge nor were ruptures seen. Pain was infrequent. Either the right, left or both ears were involved. There was often a difference in the degree of involvement between the two sides. Occasionally, the canal was involved without the drum or vice versa. When ear findings were present, they were noted on the first or second day of illness rather than appearing as a late development.

10. Glands: The cervical glands were enlarged in 80% of the patients. The superior part of the posterior chain of this group was most commonly involved. These were located along the superior posterior border of the sternocleidomastoid muscle. While most of the glands were the size of peas, a few were much larger. The cervical glands were nontender or only slightly tender. The tonsillar glands were palpable in 60% of

the patients. They were not as large as those of the upper-posterior cervical chain. The preauricular glands were enlarged in very few patients. However, in one of our cases the presenting complaint on admission was pain in the left preauricular gland associated with mild, unilateral conjunctivitis. This gland increased in size during the course of the illness causing a mild temporary facial-nerve paralysis.

Generalized lymphadenopathy, i. e., axilliary, inguinal, cervical, epitrochlear, preauricular, and submental, was present in about 10%-15% of the patients. These percentages on generalized lymphadenopathy may be too low. During the early course of the epidemic, the diagnosis of APC III infection was not established and our main concern was poliomyelitis. At that stage neurological examination was of greater importance to us than the presence of lymph nodes.

11. Lower Respiratory Tract: Most of the pathology was present in the nose and throat. In only one patient was cough a troublesome symptom. No abnormal physical signs could be detected on percussion or ausculation of this patient, and the cough disappeared after six days. Two children, who had been troubled with moderately severe chronic bronchial asthma, were temporarily relieved of their wheezing during their acute attack of pharyngoconjunctival fever.

12. Abdomen: Abdominal symptoms were noted in about 22% of the patients. This consisted of nausea, vomiting, or mild abdominal discomfort. Slight tenderness was elicited only rarely over the liver region. Hepatomegaly with or without splenomegaly was found in about 18% of the patients. Splenomegaly was present in 12% of the patients and was always associated with hepatomegaly. In several of the younger children the liver was enlarged to 4-5 fingerbreadths below the costal margin. The spleen was not larger than 1-2 fingerbreadths below the costal margin. Enlargement of the liver usually persisted for a few days. In a few patients whose convalescence was marked by lethargy and anorexia, persistence of hepatomegaly was noted for as long as three weeks. Hepatomegaly was usually associated with generalized lymphadenopathy.

13. Neuromuscular: Slight to moderate nuchal rigidity, lumbar stiffness, and Kernig's reaction were noted in 18% of the patients. In three cases neck stiffness was the presenting complaint. These symptoms persisted for 24-48 hours after admission to the infirmary. During the early phase of our epidemic before the diagnosis of APC III infection was established, one of our campers was sent to a neighboring hospital with a possible diagnosis of poliomyelitis being entertained. Spinal tap was negative, and the patient continued to run a course typical of pharyngoconjunctival fever.

TABLE 1.—*Signs and Symptoms Found in One Hundred Thirty Patients During Epidemic of Pharyngoconjunctival Fever*

A. Subjective Complaints:	
1. Malaise	81%
2. Headache	65%
3. Eye Discomfort	15%
4. Rhinorrhea or nasal obstruction	12%
5. Throat discomfort	86%
6. Ear discomfort	3%
7. Abdomen	
a. nausea	22%
b. vomiting	8%
c. discomfort	19%
8. Muscle tenderness	8%
B. Physical Findings:	
1. Eyes	
a. injection	80%
b. granularity	70%
2. Nose	
a. injection	44%
b. obstruction	85%
c. postnasal discharge	65%
3. Pharynx	
a. duskiness of anterior pillars	40%
b. injection	45%
c. pinpoint follicules of anterior pillars	80%
d. lymphoid nodules	31%
e. encapsulated glairy exudate	35%
f. diffuse exudate	28%
g. petechiae	13%
4. Tongue—strawberry	48%
5. Ears	
a. drums—injected	27%
b. canals injected	38%
6. Glands	
a. posterior cervical	80%
b. tonsillar	65%
c. preauricular	8%
d. submaxillary	3%
e. epitrochlear	15%
f. axillary	15%
g. inguinal	10%
7. Abdomen	
a. tenderness	8%
b. hepatomegaly	18%
c. Splenomegaly	12%
8. Neuro muscular	
a. nuchal rigidity	16%
b. lumbar stiffness	16%
c. Kernig's	8%

A summary of the clinical symptoms and physical findings as seen in this epidemic of pharyngoconjunctival fever is found in Table 1.

14. Fever Course: The fever lasted from one to eight days with most of the cases persisting for four and a half days. The period of hospitalization ranged from two to nine days with the majority of patients remaining for five and a half days. The fever ranged from 100F to 105.5F, with the average height from 103F to 104F. A great number of patients gave a characteristic daily spiking temperature wave with 8 a.m. depressions and marked elevations at 4 p.m. or 8 p.m. This pattern persisted for about four days followed by rapid lysis. The more typical fever curve is illustrated on Figure 7. While this fever curve was frequently seen, this pattern was not a constant finding. Great variations were found on perusal of the fever charts.

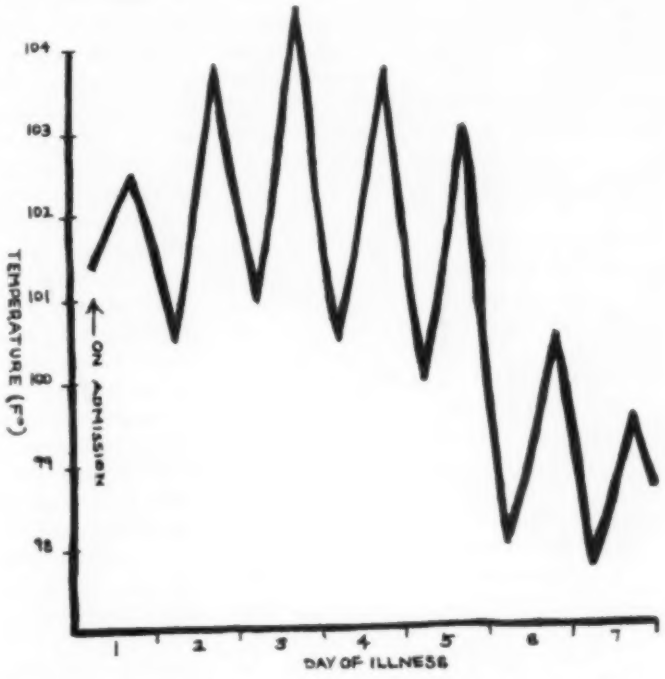

Fig. 7.—Temperature curve of a boy, age 8 years.

15. Readmissions: On the mainland camp there were 77% of the camp population who were admitted to the infirmary during the first and second wave of illnesses. Approximately 10% of the campers had more than one admission, and 2% had three admissions to the infirmary. Of the readmisions 7% had their first admission to the infirmary during the preepidemic period which was characterized by the mild pharyngitis described earlier. Their second admission was during the epidemic wave with the more typical picture of pharyngoconjunctival fever. The remaining 3% of the readmissions were sick for the first time during the second epidemic wave and had recurrences of greater or lesser severity during the second wave. The time interval between admissions varied from one day to one month.

16. Convalescence: Patients were discharged from the infirmary 24 hours after their temperatures returned to normal. The children were kept on limited activities for an additional 48-72 hours and then returned to full activities. Most of the campers responded very well on this regimen.

However 15% of the children had a more prolonged convalescence. They remained listless, anorexic, they fatigued easily, their skin was clammy, and they had occasional attack of syncope. Because of syncope, EKG's were done on 12 patients who had prolonged convalescent periods. No abnormal significant findings were noted. Generalized lymph adenopathy and hepatomegaly were noted in most of these slow convalescers. The prolonged convalescence persisted from one to three weeks. However, at the end of the camp season on August 25th all these children appeared fully recovered.

17. Response to Medication: Various medications were employed. Penicillin, sulfisoxazole, tetracycline (Achromycin), and erythromycin were used singly and in various combinations. Table 2 shows the various drugs employed and the duration of illness. The duration of illness was from the day of infirmary admission to the day of discharge. Discharge of the patient occurred usually after 24 hours of normal temperature. There was no effect upon the length of illness between different medications and when no drugs were used. The average duration of illness without the use of medications was 4.14 days, which was slightly lower than when drugs were employed. At the early part of the epidemic, the disease was not diagnosed and various medications were tried. Even as we began to suspect the true nature of the illness, it was difficult to abstain from the use of the "miracle" drugs when the temperature rose above 104F. Concern about possible complications with such temperatures made for more liberal use of antibiotics. As a result, the control group that was not given any medication contains less severely ill campers. This may account for a slightly shorter course of illness when no drugs were used. When the true clinical picture of pharyngoconjunctival fever was recognized, one of the pharmaceutical companies § contributed a generous supply of erythromycin. We placed alternate patients on this drug but could not detect any beneficial effect from erythromycin on the duration of illness. A group of 25 campers were placed on prophylactic erythromycin to note the possible therapeutic effect on preventing the disease. No beneficial effect could be noted on the early use of this medication. An equal number of control and medicated campers showed development of the illness despite early use of erythromycin.

TABLE 2.—*Comparison of Different Therapies on Duration of Illness in Pharyngoconjunctival Fever*

Therapy	Total No. Pts. in group	Mean days in Infirmary
Penicillin	55	5.35
Sulfasoxazole	11	5.55
Penicillin and eryth.	3	7.33
Sulfasoxazole and eryth.	1	5.0
Tetracycline	1	7.0
Penicillin, sulfasoxazole and tetracycline	1	7.0
Penicillin and sulfasoxazole	26	5.69
Erythromycin	21	4.86
No Drugs	37	4.14

Various eye medications were used, i. e., sodium sulfacetamide (Sulamyd), sulfisoxazole, oxytetracycline (Terramycin), tetracycline, corticloron, and hydrocortisone. Slight symptomatic relief was obtained from hydrocortisone eye drops. No eye medication prevented the unfolding of generalized syptemic manifestations despite the early use of the drugs, i. e., nasal decongestants, racephedrine (Ephedrine), phenylephrine hydrochloride (Neosynephrine), cortisone, and cortisone plus antibiotics, were largely ineffective in relieving the nasal blocking which was such a troublesome symptom during the course of the disease.

18. Blood Studies: The literature reports an initial slight leucocytosis followed by slight leucopenia with relative lymphocytosis.

§ Erythromycin was supplied by Abbott Laboratories, Chicago.

We were unable to repeat the studies on complete blood counts because of lack of laboratory facilities at camp. One patient was admitted to the local hospital with a diagnosis of poliomyelitis being entertained. The total white blood count was 12,000 with a differential count of polymorphonuclear 72 and lymphocytes 28. Blood smears were taken on 15 acute and convalescent patients and sent to the neighboring hospital for study. A few patients had a slight preponderance of polymorphonuclears, but the majority had either an equal number of polymorphonuclears and lymphocytes, or slight lymphocytosis. A few patients had an increased number of monocytes and several atypical lymphocytes but not typical of infectious mononucleosis.

Additional blood studies were done to rule out other diseases. Heterophile, typhoid, paratyphoid, and leptospira agglutinations were negative in five patients. The thymol turbidity showed one- to two-plus reaction in four out of five patients. The cephalin reaction was two plus in one of these five patients and negative in the others. Other liver function tests were not performed.

19. Bacteriological Studies: Throat cultures were taken on six patients at the height of the epidemic on August 8th. Some of the throats appeared more injected at this time than previously observed. The laboratory reported the presence of Streptococcus hemolyticus. It was felt that this was a secondary invader since there had been no clinical response to sulfasoxazole, penicillin, or a combination of the two drugs. Nevertheless, all personnel of the camp were placed on prophylactic sulfasoxazole in dosage of 1 gm. daily for three days. Administration of sulfasoxazole did not alter the course of the viral epidemic. Repeat throat cultures taken five days later revealed only 3 out of 16 patients with Str. hemolyticus. Third throat cultures repeated a week later were reported negative for hemolytic Streptococcus.

Eye cultures were taken on 15 patients with conjunctivities. No bacterial growth was observed. No study for inclusion bodies was made.

20. Viral Studies: Smears were taken from conjunctiva, throat, and rectum of 10 acutely ill patients. We attempted to isolate the virus but, because of lack of personal experience with the He La cells, had great difficulty in growing the virus. Dr. Robert Huebner, Chief of the Section on Virus and Rickettsial Diseases, National Institute of Health, Bethesda, Md., kindly consented to do our viral studies. Identification of APC Type III was successful in 8 out of the 10 patients. Heavy growth was reported from most of the specimens. In several patients the virus was obtained from all three sources. Other pathological viruses were sought for but none were found.

There were 21 samples of blood taken from acute and convalescent patients. These were not paired sera. These sera were sent to the National Institute of Health at Bethesda. Complement fixation studies against Type III antigen was performed. Almost all of the convalescent sera had a complement antibody rise above 64. The majority of the acute sera showed much lower titers. It was their opinion that there was a very significant rise of antibodies shown in the convalescent patients. Neutralization studies were not performed on the sera because of the vast amount of work involved in that particular test. Furthermore, the presence of APC III virus in the conjunctiva, throat, and stool in such overwhelming number was conclusive evidence of the nature of the illness.

Comment

A comparison of the clinical findings in the other reports as compared with our epidemic is seen in Table 3. The major features are identical, i. e., pharyngitis, conjunctivitis, rhinitis, cervical lymphadenitis, and fever. There were additional findings in our epidemic which were not mentioned or frequently found in the other studies. These differences will be discussed in greater detail in the following paragraphs.

TABLE 3.—*Comparison of the Clinical Signs and Symptoms Found in Previous Reports of Pharyngoconjunctival Fever*

Article	Pharyngitis	Conjunctivitis, Unilateral or Bilateral	Rhinitis	Spiking Fever 3-7 Days.	Cervical Adenopathy	Generalized Glandular Adenopathy	Hepatomegaly	Splenomegaly	Meningismus	Summer Season	Epidemic Nature
Derrick (Australia) 1943	+++	+++	+++	+++	?					+	
Cockburn (Greeley's disease, Colorado, 1951)	+++	+++	+++	+++	?				+	+	+++
Parrott, Rowe, Huebner et al. (hospital outbreak) Feb., 1954	+++	+++	+++	++	++		+			Feb.	+
Bell, Rowe, Huebner et al. (Va. Day Camp 1954)	+++	+++	++	++	++					+	+++
Wallis, Carlisle, Eng., 1955	+++	+++	++	++	++				+	March -April	+++
Sobel, Aronson, and Walker, 1955	+++	+++	++	++	++	+	+	+	+	+	+++

Hepatomegaly and splenomegaly were present in about 18% of our cases. This finding was found in only one of the five previous reports. Generalized lymphadenopathy was present in 10% of our patients. This was not noted previously. Cervical lymphadenitis was a frequent finding in all the previous records. However, the superior part of the posterior chain was the site of greatest hypertrophy in 80% of our patients. This virus appeared to have a predilection for lymphoid tissue throughout the body. Some of the areas which showed this hypertrophy were the lymphoid follicles of the conjunctiva, papillae of the tongue, lymphoid follicles of the anterior pillars of the tonsils, adenoids, postpharyngeal lymphoid tissue, generalized peripheral lymph glands, blood, liver, and spleen.

Meningismus was present in 16% of our patients. This was noted in only one other report in the literature. The presence of meningismus in several of our cases before the clinical diagnosis of pharyngoconjunctival fever was established proved a very disturbing finding. One of our early cases was admitted to a neighboring hospital with a tentative diagnosis of poliomyelitis. Similar difficulty in misdiagnosing some cases of APC fever as poliomyelitis was reported in Cockburn's article from Greeley, Colo. It is hoped that knowledge of the possibility of the existence of this neurological finding will spare other workers our early anxiety and concern.

No complications or involvement were noted in the lower respiratory tract in this disease. In contrast to the virus of the common cold, this APC III virus produced a temporary beneficial effect on bronchial asthma. Wheezing was alleviated temporarily during the acute illness. Complications other than secondary infection of the nasal passages were not seen. The presence of auditory canal and drum involvement were noted in the Virginia day camp epidemic as well as in ours. It is our impression that this was part of the disease rather than a secondary involvement since these findings were present on admission rather than developing at a later date.

A small number of our campers had a prolonged convalescence. The only other report on delayed convalescence following an attack of pharyngoconjunctival fever is found in a Wallis' report in Carlisle, England. A small but very definite percentage of Wallis' cases had a very slow convalescence marked by listlessness, fatigue, and anorexia.

Another difference from other reports was the occurrence of readmissions. There was a total readmission rate of 10%, of which 7% had their first admission during the first wave and second admission during the second wave, and 3% had readmissions limited to the second wave. The other literature does not comment on readmissions.

In previous reports isolation of APC III virus from pharynx, conjunctiva, and stool has been successful in patients with pharyngoconjunctival fever but no growth has been obtained from healthy contacts. No virus and no acute and convalescent antibody studies were done on the contacts in this epidemic. Many of these clinically well people showed a fine follicular hypertrophy of the anterior pillars of the tonsils and granularity of the palpebral conjunctive which were seen so commonly in the sick patients. It was our impression that some of these contacts had subclinical infections. Perhaps in previous investigative work, the virus concentration in these contacts was too low for successful growth.

Diseases to be considered in the differential diagnosis of pharyngoconjunctival fever are nonpurulent conjunctivitis, herpangina, streptococcal pharyngitis, influenza, leptospirosis, non-bacterial-exudative pharyngitis, anicteric jaundice, infectious mononucleosis, poliomyelitis, and two recently reported epidemics of unknown etiology.

Epidemic keratoconjunctivitis and inclusion conjunctivitis have similar conjunctival findings but are not associated with generalized symptoms.

Leptospirosis is a severer illness, with high mortality, high incidence of jaundice,

and in which agglutination tests are positive.

Infectious mononcleosis does not have the conjunctivitis; the blood smear and heterophile agglutination are confirmatory findings.

Influenza does not show the conjunctivitis seen in pharyngoconjunctival fever.

Herpangina is characterized by herpetic rather than follicular lesions of the soft palate and anterior pillars of the tonsils, and by the absence of conjunctivitis.

Non-bacterial-exudative pharyngitis ‖ is probably due to APC TYPE IV virus. Hilleman's R1-67 virus is identical with APC IV virus. Pharyngeal findings are similar to those found in pharyngoconjunctival fever. The duration of illness, spiking fever, clearing by lysis, pharyngeal findings are the features in common. They are differentiated by the absence of conjunctivitis and specific neutralization studies.

In Streptococcus pharyngitis the pharynx is redder; there is greater edema; the duration of illness is usually less than four days with excellent response to sulfonamide compounds and the antibiotics; the exudate is occasionally more yellow, larger in extent, and frequently confluent in one or more areas. In nonstreptococcal or viral pharyngitis the exudate is white or gray, pinhead or slightly larger in size, distributed over enlarged lymphoid follicles on the posterior pharyngeal wall and in the crypts of the tonsils, and encapsulated glairy material may be present.

Anicteric jaundice [21] presents a similar pharyngeal picture, similar spiking fever course of the same duration as pharyngoconjunctival fever. In contrast, there is no conjunctivitis and hepatomegaly is a more frequent finding.

Poliomyelitis produces paralysis in a certain percentage of cases during an epidemic, and the spinal fluid changes are characteristic.

A recently reported epidemic in London [22] has certain clinical similarities to the APC III type of infection. This epidemic affected more than 100 adults and necessitated the closing of a hospital. It was characterized by pharyngitis, posterior cervical lymph node enlargement, occasionally generalized lymphadenopathy, hepatosplenomegaly, muscular pains, and pyrexia, but differed in the absence of conjunctivitis and presence of temporary mild paresis.

Another recently reported clinical entity from Peru [23] has many similarities to the APC III infection. This Peruvian disease was characterized by pyrexia, pharyngitis, generalized lymphadenopathy, hepatosplenomegaly, slight leucocytosis followed by leucopenia with relative lymphocytosis, predominance in young children, and unresponsive to any drugs. It differs from APC III infection mainly in the absence of conjunctivitis.

An accurate clinical diagnosis of isolated cases of pharyngoconjunctival fever is difficult to make in the absence of an epidemic, particularly if conjunctivitis is absent. In the presence of an epidemic the diagnosis is easily established by the presence of conjunctivitis (frequently unilateral in onset), pharyngitis, rhinitis, and cervical adenitis, or any combination of these symptoms. Isolation of the APC III virus and specific antibodies during the convalescent period are important laboratory confirmation.

The epidemology in our outbreak is similar to reports of other epidemics in the literature, i. e., the predominance in the younger age group, occurrence in summer months, and explosiveness of the outbreak. Many of the other reports have speculated on the role of the swimming pool as the common source of contact; however, there was no swimming pool in our camp. From a study of the bunk distribution and the rate of new admissions it appears most likely that spread was through droplet infection. It is interesting to speculate on the relationship of the first and second wave of illness. The first wave was characterized by a mild pharyngitis. The infirmary admission rate during the first three weeks of camp was higher than the total summer

‖ References 17-20.

admission rates for other years. Toward the end of the first minor wave of illness, a consultant was called into camp to study the high incidence or respiratory infections. It is interesting to note in retrospect that, although he could not diagnose the type of upper respiratory infection, he did predict the occurrence of a second larger outbreak followed by a third smaller wave. Fortunately the camp closed on August 25th at the end of the second wave so that his complete predictions were not realized. The findings in the pharynx during the first wave were similar to that found during the second epidemic period. There was a fine follicular hypertrophy and duskiness of the anterior pillar, but exudate and glairy material were not seen. The conjunctivitis was present in a very small number of cases, and the entire clinical course was very mild. These cases could have been overlooked very easily had it not been for the overzealous care given by the medical staff. This first minor wave of illness preceding the major epidemic was not reported in other articles. It is possible that the first wave may have been overlooked in other epidemics. This preliminary mild pharyngitis may represent a forerunner to the later explosive outbreak and may serve as the first danger signal. On the other hand, this first wave may bear no relationship to the second wave. The first wave may be due to a different virus and unrelated to the main epidemic. It is our opinion that there is a relationship between the two waves.

Inquiries in the neighboring communities revealed that there was occurrence of pharyngoconjunctival fever within a radius of 150 miles. A Maine boys camp accommodating 200 children and located 100 miles from our study reported by personal communication a similar epidemic of equal magnitude.

Preliminary reports reveal the efficacy of a vaccine[7] for APC III infection. Few people have protection against APC III according to antibody studies in the adult population. Should immunization be recommended when this becomes available?

Summary

An epidemic of pharyngoconjunctival fever occurred in a summer camp for boys. It was characterized by spiking fever of three-seven days duration usually terminating by lysis, unilateral or bilateral follicular conjunctivitis, follicular hypertrophy of the anterior pillar of the tonsils, enlargement of the nasopharyngeal lymphoid tissue, and cervical adenitis. Less common findings were generalized glandular enlargement, hepatomegaly, splenomegaly, and meningismus. Convalescence was occasionally prolonged. There were great variations present in these clinical findings. There was a heavy growth of APC III virus isolated from the conjunctivae, throat, and stools of 8 out of 10 patients studied. A significant rise of complement fixing antibodies was noted in the convalescent sera. The disease occurred in an explosive manner over a three-week period in August, 1955. It involved 62% of the campers, and 10% of the counselors. It was preceded by a smaller wave in July characterized by a mild pharyngitis. This involved 36% of the campers and 13% of the counselors. The relationship between the two waves is not known. The disease affected mostly younger children and appeared to be spread by droplet infection. Chemotherapy was ineffective.

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Abstracts from Current Literature

Journal of Clinical Investigation, New York

35:355-452 (April) 1956

* Familial Hypolgycemia Precipitated by Amino Acids. W. A. Cochrane, W. W. Payne, M. J. Simpkiss, and L. I. Woolf.—p. 411.

Familial Hypoglycemia Precipitated by Amino Acids.—Three cases of spontaneous hypoglycemia in one family, and one unrelated case, were shown to be induced by the administration of L-leucine or isovaleric acid. Two cases in the family, infants with typical hypoglycemic seizures, became symptomatic after weaning from the breast. In the one explored the pancreatic islet cells were normal. Insulin-like activity of the blood in both was normal. The third case in this family was the father of these patients. He was symptom free but had convulsions as an infant and until 13 years had many episodes of abnormal sleep lasting from a few moments to 4 days. Fasting blood sugars at 27 years of age were 64, 46, and 48.5 mg/100 cc. The fourth case, an infant with typical hypoglycemic seizures since 2 months of age, had preprandial sugars of 35-45 mg/100 cc. and insulin-like activity of the blood six times normal. Despite partial pancreatectomy and cortisone for eight months, he continues to have occasional seizures and is grossly retarded.

Clinical observation in the past had suggested that many instances of idiopathic hypoglycemia would respond to diets low in carbohydrate and high in protein. Several published cases, however, have shown that some cases will become worse under this regimen. In these cases it was also true. The patients had become worse on high protein diets, especially when weaned from human to cow's milk. Test doses of casein produced a fall of 20-25 mg/100 cc. in the fasting blood sugar within one hour, and a corresponding rise in amino acid levels. This fall was not found in control subjects (although the amino acid rise was similar). The result established a causal relationship between protein feeding and hypoglycemia.

In an attempt to determine whether this was due to protein in general or a particular group of amino acids, gelatin was also fed. It produced a minor change in blood sugar. Tyrosine, which is almost absent from gelatin but comprises 6.4% of casein, was tried and produced no change. L-leucine was next investigated and produced a most dramatic effect, the extent of the response varying with the dose. Generally, with 150 mg/kg. the blood sugar values fell to one-half the fasting levels in 30-45 minutes. Clinically, the responses varied from marked pallor and drowsiness to actual convulsions which required glucose administration for cure. Normal subjects showed no such response. Isovaleric acid produced a blood sugar fall similar to that of L-leucine. The authors feel that this amino acid is the true hypoglycemic factor in these patients and that leucine acts by reason of its rapid conversion to isovaleric acid.

On investigation the patients showed no evidence of liver, pituitary, thyroid, or adrenal abnormalities. In one case with hyperplasia of islet cells of the pancreas there was a high blood insulin-activity level, but clinical responses to the amino acids were identical with those seen in the other three patients. The effects produced by Adrenalin and Glucagon (hyperglycemic-glycogenolytic factor of the pancreas) in all cases were normal.

The blood sugar curve after leucine closely resembles that of the normal person during an insulin tolerance test. The authors therefore suggest a diagnostic test consisting of the feeding of casein (1.5 gm/kg.) or L-leucine (0.15 gm/kg.) to the fasting subject and measuring blood sugars at frequent intervals for 90 minutes, in all cases of spontaneous hypoglycemia.

The Journal of Pediatrics, St. Louis

48:129-278 (Feb.) 1956

The Effect of Reserpine and Its Combination with Hydralazine on Blood Pressure and Renal Hemodynamics During the Hypertensive Phase of Acute Nephritis in Children. J. N. Etteldorf, J. D. Smith and C. Johnson.—p. 129.

Acerola Juice—The Richest Known Source of Vitamin C. N. W. Clein.—p. 140.

* Antibiotics and Chemotherapeutic Agents in the Treatment of Uncomplicated Respiratory Infections in Children. L. M. Hardy and H. S. Traisman.—p. 146.
Toxicity Due to the Use of Tyzine Hydrochloride. W. K. Brainerd and R. W. Olmsted.—p. 157.
Hyaline Membrane Disease of Lungs. M. J. G. Lynch and L. D. Mellor.—p. 165.
Failure of Hyperthermia to Activate Experimental Epileptogenic Foci in Monkey. R. P. Schmidt, A. A. Ward and W. J. Wolfe.—p. 180.
Growth Curves of Height and Weight by Age for Boys and Girls, Scaled According to Physical Maturity. N. Bayler.—p. 187.
Geographic Variations of Dental Caries in Oregon. VII. Caries Prevalence Among Children in the Blue Mountains Region. D. M. Hadjimarkos.—p. 195.
Bilateral Adolescent Mammopathy as a Presenting Symptom of Rhabdomyosarcoma of the Heart. G. Manson and W. Rindskoff.—p. 202.
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Congenital Heart Block. A. J. Moss and N. N. Litman.—p. 226.
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The Uses of Chlorpromazine in Pediatrics. H. Bakwin.—p. 240.
A Psychosomatic Study of Five Children With Duodenal Ulcer. A. H. Chapman, D. G. Loeb, and J. B. Young.—p. 248.

48:545-692 (May) 1956

A Study of Hemolytic Streptococcal Infections in Relation to Antistreptolysin O Titer Changes in Orphanage Children. H. Packer, M. B. Arnoult, and D. H. Sprunt.—p. 545.
Management of Foreign Objects in the Alimentary Tract. H. I. Laff and R. P. Allen.—p. 563.
Intracutaneous Asthma Vaccine Therapy in Asthmatic Children: Its Application and Clinical Value. L. Tuft and F. Ermilio.—p. 569.
Microchemical Blood Standards for Normal 5-Day-Old Newborn Infants. M. L. Spivek.—p. 581.
Clinical and Laboratory Evaluation of Acetylsulfisoxazole (Acetyl-Gantrisin) in Children. S. Hagler, A. Kaufman, E. Kaiser, M. Lillien, and H. McClain.—p. 588.
A Study of the Association of Prenatal and Paranatal Factors with the Development of Tics in Children. B. Pasamanick and A. Kawi.—p. 596.
Hyaline Membrane Disease. M. J. G. Lynch, L. D. Mellor, and A. R. Badgery.—p. 602.
Hypoplasia of the Pituitary and Adrenal Cortex. H. D. Mosier.—p. 633.
Incidence of Retrolental Fibroplasia: Past and Present. T. M. Shapira, S. M. Schall, H. Feinhandler, and D. Kane.—p. 640.
Children with Muscular Dystrophy. H. M. Wallace, M. Lending, and H. Rich.—p. 658.
* Psychotic Reactions Occurring in 2 Adolescent Girls During Treatment with ACTH and Cortisone. H. M. Adams, R. A. Jensen, and R. A. Good.—p. 667.

48:693-838 (June) 1956

* Acute Barbiturate Poisoning—How Should It Be Treated? J. K. Wilson.—p. 693.
* Editorial Comment on the Treatment of Acute Barbiturate Poisoning. J. N. Etteldorf and R. A. Woodbury.—p. 698.
The Effect of Specific Therapy in Primary Tuberculosis of the Child. A. Robinson and M. Meyer.—p. 705.
Chronic Benign Neutropenia in Infancy and Early Childhood. T. D. Stahlie.—p. 710.
Absorption of Oily and Aqueous Preparations of Tetracycline in Children. B. Miller and W. E. Clapper.—p. 722.
The Daily Circulating Eosinophil Response as a Guide to Adequacy of Hormone Therapy in Active Rheumatic Carditis. W. N. Lim.—p. 725.
Consequences of Neonatal Pathology. H. E. Thelander, E. Cabos, and A. Gerhard.—p. 731.
Infantile Cortical Hyperostosis. F. Brooksaler and J. E. Miller.—p. 739.
A New Quantitative Approach to the Study of Anthelminthic Drugs, with an Evaluation of Piperazine Hexahydrate, Phthalylsulfathiazole, and RO 2-5655/3 in the Treatment of Enterobius Infection. E. H. Sadun, D. M. Melvin, M. M. Brooke, and C. H. Carter.—p. 754.
The Treatment of Wilms' Tumor. E. Ng and B. V. A. Low-Beer.—p. 763.
The Influence of Breast Feeding on Weight Gain in Infants in the First Year. J. Millis.—p. 770.
Transient Synovitis of the Hip. N. J. Rosenberg and E. E. Smith.—p. 776.
Hypopituitarism, Hypoadrenalism, and Hypogonadism in the Newborn Infant. R. M. Blizzard and M. Alberts.—p. 782.
Meconium Peritonitis: A Surgical Emergency. R. B. White.—p. 793.
Arthrogryposis Multiplex Congenita. R. M. Fitti and T. M. D'Auria.—p. 797.

Antibiotics and Chemotherapeutic Agents in the Treatment of Uncomplicated Respiratory Infections in Children.—Despite frequent admonitions, the practice of treating nonspecific respiratory infections with antibiotics is widespread. The main reason for this is because the physician is afraid he may be dealing with a bacterial infection that needs treatment, or he believes antibiotic therapy will prevent any secondary bacterial complication. This paper describes the course of such infections in 529 children. These children were in three groups. The first was composed of 217 children presenting at the

outpatient department of the Children's Memorial Hospital in Chicago and was treated by a double blind study with either a placebo, Gantrisin, penicillin, or Aureomycin. The second group was composed of hospitalized patients, not a controlled study, but analyzed according to therapy given. The third group was composed of private patients treated with antibiotics only if after a complication had arisen.

Because it was a controlled study, the first, or outpatient, group is of most interest. This group was treated in rotation according to a code known only to the pharmacist. If complications such as otitis media, pneumonia, etc. occurred, the type of medication was checked and changed if it were felt necessary. The incidence of complications was essentially the same regardless of the type of treatment, although the type of complication was somewhat different. In those children with an initially high white blood cell count the incidence of bacterial complications seemed higher than in those with low white blood cell counts. However, complications of a viral nature had a higher incidence in the treated group.

The authors conclude that antibiotic therapy should not be given blindly in children with respiratory infections but only at the onset of complications or possibly sooner if the initial white blood cell count is high.

Psychotic Reactions Occurring in 2 Adolescent Girls During Treatment with ACTH and Cortisone.—Two instances of severe psychotic reactions are reported in association with ACTH and cortisone therapy. One patient was a 15-year-old girl under treatment for rheumatic fever with ACTH. During the 15th week of treatment she developed personality changes followed in 4 days by a frank psychosis with delusions, disorientation, and behavior characteristic of a paranoid schizophrenic reaction with catatonic features. She gradually improved over a period of weeks. The second patient was a 17-year-old-girl with plasmacellular hepatitis treated with ACTH and cortisone. In contrast to the first girl who had a poor social and emotional background, this girl had had no significant previous emotional difficulties. ACTH had been given daily for one month and then cortisone daily for 19 months when the psychotic episode appeared after the death of a hospital friend. This reaction was characterized by disorientation, negativism, incontinence, and manic-like episodes. In association with electroshock therapy she recovered in six weeks.

The authors review the literature on mental disturbances concerning steroid therapy and feel the relationship is associated with a change in the person's response to stress. Psychiatric observations on other children receiving steroid therapy revealed less serious reactions than these in other children. The children between 10 and 16 years seemed especially vulnerable, owing to the changes of personality and hormonal balance in adolescence. This hazard of steroid therapy seems to have a good prognosis, but it is a complication that cannot be considered lightly.

Acute Barbiturate Poisoning—How Should It Be Treated?

Editorial Comment on the Treatment of Acute Barbiturate Poisoning.—These two papers present the problem of the treatment of barbiturate intoxication in a most interesting and instructive way. Dr. Wilson reports on a fatal case of barbiturate poisoning in a 4-year-old boy and tells of the confusion in the current literature regarding treatment, especially in respect to the use of analeptics. Because of these conflicting statements he asks for an opinion to help the busy practitioner suddenly faced with such a desperate situation.

Dr. Etteldorf and Dr. Woodbury, in answer to this query, review the pharmacology of barbiturate intoxication. They make the following recommendations: (1) remove any drug remaining in the stomach by gastric lavage, (2) maintain respiratory exchange preferably by a respirator and by oxygen before hypoxia occurs. It is apparent that analeptics such as metrazol and picrotoxin may be lifesaving if given in sufficient quantity to stimulate the respiratory center (0.2-0.3 mg/kg. for picrotoxin), but the administration must be continuous and overdosage may cause convulsions with deleterious effects. It is for this reason that artificial respiration is preferred with the concomitant use of oxygen. The cited danger of oxygen in a patient with severe respiratory depression need not be considered when a respirator is being used; (3) maintain circulation by agents acting directly on the smooth muscles of the arterioles such as levarterenol (Levophed); (4) maintain correct nutrition, fluid and electrolyte balance, paying par-

ticular attention to potassium if electrocardiographic or other evidence of hypokalemia is present; (5) the use of blood dialysis, peritoneal lavage, or even repeated exchange transfusions to remove circulating barbiturate should be considered in severely poisoned patients, if these techniques are available.

Medical Journal of Australia, Sydney

1:429-476 (March 17) 1956

Height-Weight Survey of New South Wales School Children. E. S. A. Meyers.—p. 435.

1:521-556 (March 31) 1956

Control of Staphylococcal Infection of the Newborn by the Treatment of Nasal Carriers in the Staff. Phyliss M. Rountree, Mary Heseltine, Judith Rheuben, and R. P. Shearman.—p. 528.

A New Method for Preventing Goitre in Canberra (the Use of Iodized Salt in Bread Baking). Eben H. Hipsley.—p. 532.

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51, No. 6 (Feb. 10) 1956

The Emaciation of Young Girls at Puberty. H. Muller.—p. 209.

51, No. 4 (Jan. 27) 1956

Hirsutism in Myxedema of Children. J. M. Cervino, J. J. Ravera, F. Rawak, A. S. Albrieux, and J. C. Mussio-Fournier.—p. 131.

51, No. 8 (Feb. 24) 1956

* Recurrent Abdominal Pains in Children. K. H. Schafer.—p. 285.

51, No. 9 (March 2) 1956

The Palability of the Appendix in Childhood and Its Diagnostic Significance. E. Smola.—p. 338.

Observations with Regard to the Picture of the Chronic Toxoplasmotic Encephalomyelitis. E. Leitritz.—p. 340.

51, No. 10 (March 9) 1956

Tuberculous Meningitis and Abacterial Nonpurulent Meningitides. H. Hilber.—p. 384.

Tuberculosis of the Bronchial Lymphnodes in Childhood and Its Differential Diagnosis. P. Zoelch.—p. 387.

Erroneous Diagnoses in cryptorchism. H. Singer.—p. 394.

Erroneous Diagnoses Round About Acetonemic Vomiting. G. Gottlieb.—p. 397.

Erroneous Diagnosis: Dystrophia Adiposogenitalis. K. Grote.—p. 400.

51, No. 11 (March 16) 1956

Investigations of the Immunizing Effect After Active Poliomyelitis-vaccination. W. Bommer, J. Stroder, and J. Friedrich.—p. 417.

Artificial Respiration in Poliomyelitis of Different Age Groups. H. Kellner and E. Sander.—p. 425.

The Treatment of Patients with Respiratory Paralysis with a Machine Other Than the Iron Lung. H. Marx.—p. 428.

51, No. 12 (March 23) 1956

The A.P.C. Virus Infection: Observations During the Epidemic in Hamburg in 1955 and of an Infection in a Family in Altona in 1956. C. Mumme.—p. 453.

51, No. 13 (March 30) 1956

* Some Considerations Concerning Blood Transfusion with Reference to the Significance of the Rhesus Factor. A. Beck.—p. 510.

51, No. 15 (April 13) 1956

Psychosomatic Medicine in Childhood. Hans Hoff and Walter Spiel.—p. 639.

51, No. 16 (April 20) 1956

* Onyalai. H. W. Snyman and A. P. McDonald.—p. 675.

Early Histological Changes in the Formation of Bone on Vitamin A Deficiency. J. T. Irving.—p. 690-693.

Treatment of Supracondylar Upper Arm Fracture in Children by Means of Nails. E. Sthamer.—p. 694.

51, No. 18 (May 4) 1956

Foreign Bodies of the Esophagus and of the Lower Air Passages. G. Eigler and W. Schweckendiek.—p. 752.
Midbrain Implantation in Encephalopathics and Debility of Different Origin in Children. Georg Destunis and Ernst Schmidt.—768.

51, No. 19 (May 11) 1956

Therapy with ACTH, Cortisone and Derivatives of Cortisone. K. Stuhlfauth, K. Bogner, A. Englhardt-Golkel, R. Prosiegl, and J. Woller.—p. 811.

Recurrent Abdominal Pains in Children.—The various aspects of unbilical colic are reviewed, with special reference to organic lesions which may have to be considered. Recurrent abdominal pain in children can occur with various diseases of the gastrointestinal tract and the mesenteric lymph glands subdivided into seven groups. Diseases of the urinary tract, of liver and biliary tract may have to be included as well as hemolytic crisis. Functionally determined are idiopathic umbilical colic, abdominal migraine, and abdominal epilepsy.

Some Considerations Concerning Blood Transfusion with Special Reference to the Significance of the Rhesus Factor.—The author summarizes his experience with 18,000 transfusions over a period of 30 years. It is concluded that the so-called Rhesus factor cannot be held responsible for untoward reactions. Only unchanged whole blood was used, and its passage from the vessel of the donor to that of the recipient took about one second using pumping compression of a tube. It is suspected that the reactions regarded as Rhesus conditioned are produced by changes in the blood while out of contact with the vessels. For the scientific evaluation of the cause of reactions an accurate description of the method of transfusion and the condition of blood or plasma is regarded as of the utmost importance. The difficulties of maintaining the prevailing hypothesis for the causation of erythroblastosis fetalis are discussed, keeping in mind that the Rhesus factor is of no importance for fresh blood transfusion.

Onyalai.—Onyalai is a special form of thrombocytopenic purpura seen nearly exclusively in Negroes "Bantu." It goes under various names in various tribes. It does not seem to occur in American Negroes. Some 7 or 8 of the 36 cases were below 15 years of age and only one below 10 years of age. The disease occurs mainly in young males. On the whole the clinical picture is similar to morbus werlhofi. Indefinite prodromal signs and abdominal pains may precede bleeding from gums, buccal and nasal mucosa, and intestinal, renal, and skin bleeding may occur. At postmortem examination hemorrhage can be seen most anywhere. Cerebral hemorrhage may be the cause of death. External bleeding is usually due to persistent seepage which may lead to considerable anemia in one or two days. Blood blisters of various sizes are seen particularly in mouth, nose, and pharynx. Loss of blood may lead to shock. The rest of the physical examination may be negative. The spleen was not palpable in any of the patients. Nearly all cases occurred during the warm months. Two patients died. The thrombocyte count was below 60,000 in the great majority the highest was 109,000 the lowest below 30,000. The number of platelets reached normal in 10 days to a few weeks. In a few cases none or only a little increase was noted in many months. Thrombocytopenia was the only defect of the mechanism of coagulation. In some cases the fragility of the capillaries was increased. The bone marrow showed only a hyperplasia of megacaryocytes. The etiology is unknown. There is no specific therapy. Transfusions improve the anemia. The acute thrombocytolysis usually runs a benign course.

Therapy with ACTH, Cortisone and Derivatives of Cortisone.—This review deals with one of the subjects of the 62nd meeting of the Society for Internal Medicine. In a table of indications the diseases are listed where the therapeutic indications for the use of these substances is assured. Another column lists the diseases where an improvement of accompanying symptoms has been registered while the third column concerns itself with such ailments where indications for this therapy are not certain.

Monatsschrift für Kinderheilkunde, Berlin

103, No. 11 (Nov.) 1955

Studies Regarding Structure and Storability of Frozen-Dried Human Breast Milk. Carl-August Sager.—p. 469.
The Question of Allergic Processes in Rheumatic Joint Diseases. Friedrich Hosemann.—p. 471.
About "Pseudo-Little's Disease" and Its Developmental Pattern in Infants. Hans Schlack.—p. 475.
* Protracted Course of Icteus Gravis Nonatorum and Its Treatment by Exchange Transfusion. Klaus Betke.—p. 477.
Differential Diagnosis of Hemophilic Joint Diseases in Children. Gerd Schroeder.—p. 480.
Fasciolosis As a Cause of Hepato-Splenomegaly. Karl Grote.—p. 482.
The Respiratory System: Review Article. H. Hilber.—p. 491.

Proctracted Course of Icterus Gravis Neonatorum and Its Treatment by Exchange Transfusion.—The fate of a child with erythroblastosis fetalis with severe jaundice is generally decided within the first 48 hours of extrauterine existence, because by this time irreparable damage has been produced if the process is sufficiently severe. Exchange transfusion in such infants should be started within the first 24 hours. This general rule should not be interpreted, however, to mean that an exchange transfusion is necessarily useless after this period has elapsed.

The author presents three cases that demonstrate that an exchange transfusion can be effective at a later period. In the first of the three infants who had Rh incompatibility, signs of erythroblastosis were not yet present on the third day after delivery. Then jaundice appeared; it became constantly severer, and the child gradually became drowsy and died in coma with signs of sepsis. The author believes that this child might have been saved by an exchange transfusion at a later date than is generally assumed effective.

In the second child, also with an Rh incompatibility and symptoms greatly resembling those of the first child, exchange transfusion was performed on the sixth day. The child recovered completely and showed no residual changes at one year of age.

The third child was afflicted with group A incompatibility. In this patient a gradually deepening jaundice accompanied by severe impairment of the general condition became evident more than one week after delivery. An exchange transfusion was carried out on the 16th day of life with rapid improvement thereafter.

Radiology, Syracuse, N. Y.

65:325-488 (Sept.) 1955

* Neuromuscular Disorders of the Urinary Tract in Children. R. Parker.—p. 325.

66:169-324 (Feb.) 1956

Unilateral Calcification of the Choroid Plexus in a Child. George Teplick and Bernard P. Adelman.—p. 231.

66:325-488 (March) 1956

* Cranial Manifestations of Familial Metaphyseal Dysplasia. Paul A. Mori and John F. Holt.—p. 335.
Selective Angiocardiography in Infants and Children. Richard D. Rowe, Peter Vlad, and John D. Deith.—p. 344.

66, No. 4 (April) 1956

* Meconium Ileus: A New Roentgen Sign. Harvey White.—p. 567.

66, No. 5 (May) 1956

The Hypothyroid Infant and Child: The Role of Roentgen Evaluation in Therapy. Lee B. Lusted and Donald E. Pickering.—p. 708.

Neuromuscular Disorders of the Urinary Tract in Children.—Of 38 cases of megacolon examined, cystograms or pyelograms were available in only 14 of which 10 had neurogenic dysfunction of the bladder. Of these five had urinary-tract symptoms. In two others such symptoms developed and abnormal pyelograms were obtained subsequent to corrective surgery for megacolon. All cases of megaloureter were associated by bladder abnormality. Out of 2430 pyelograms and cystograms, a possible neurogenic disease of

the bladder or ureters was present in 35. All but 14 had mechanical obstruction. This demonstrated the rarity of primary megaloureter.

The abnormal physiology, pathology and treatment are discussed. Pyelograms of seven cases are included in this report.

Cranial Manifestations of Familial Metaphyseal Dysplasia.—Recent observations indicate that familial metaphyseal dysplasia (Pyle's disease) which is characterized by idiopathic symmetrical splaying of the tubular bones is not as rare as previously supposed and that strikingly characteristic cranial manifestations may accompany the metaphyseal splaying. Bone of purely membranous origin (flat bones of the skull) or of partly membranous origin (base of skull, face, and mandible) shows a fairly uniform hyperostosis. Endochondral bones with profound growth tendencies (the appendicular skeleton) reveal a failure of modeling but no hyperostosis. Endochondral bones in which little growth occurs (sternum, epiphyses of all long bones, vertebral bodies, tarsal and carpal bones) show no roentgen abnormality. The clinical features depend entirely on the osseus changes.

Knock-knees, limitation of extension of the elbows (due to metaphyseal widening), delayed dentition, palpable fusiform enlargement of the lower portion of the femurs and upper tibias, and disproportionately long lower extremities represent the clinical findings. Laboratory examinations have been normal. Pathological fractures have occurred but there was no delay in healing.

In the presence of hyperostosis of the skull there is enlargement of the head and mandible, hypertelorism, broad flat nose, and cranial-nerve abnormalities due to narrowing of the cranial foramina. In all of the cases reported by the authors hearing loss was present. Visual loss, epiphora, and facial paralysis were present in one.

The prognosis depends on the extent of cranial involvement. General health is otherwise unimpaired.

Until more is known of the processes involved in bone matrix formation and resorption, the etiology and pathogenesis of this entity will remain an enigma.

Meconium Ileus: A New Roentgen Sign.—In 10 cases of meconium ileus 4 were complicated by volvulus, gangrene, or peritonitis and came to surgery and autopsy. All were proved cases of fibrocystic disease. Of six uncomplicated cases two died after laparotomy, and autopsy confirmed the diagnosis of fibrocystic disease. The remaining four patients survived after the surgical removal of the meconium plug and introduction of panteric granules into the small bowel. One of these died months after leaving the hospital from intestinal obstruction. The three remaining cases are reasonably well.

The roentgen findings were constant in the uncomplicated cases. Dilated loops of small bowel were demonstrated in the supine position, indicating the presence of ileus, but in the upright position fluid levels were either absent or present in an insignificant degree. This was contrary to the usual findings in obstructive ileus. The duration of the obstruction did not appear to be a contributing factor.

Theorizing on the change in the x-ray appearances in uncomplicated meconium ileus, certain physiologic disturbances were considered. It is known that gas accumulates in obstructions in three and one half hours, and the accumultaion of fluid seems to be the result of increased secretion and diminished absorption from the mucosa of the bowel. The meconium is removed with considerable difficulty because of its sticky mucilagenous nature. Interference with the normal physiology is considerable. Mucosal secretion may be prevented or at least diminished as compared with the common type of mechanical obstruction. Also there is evidence of disturbed duodenal secretion of children with fibrocystic disease.

The above mentioned conditions seem to offer an explanation for the absence of fluid levels, an important diagnostic sign in common obstruction, on abdominal roentgenograms in uncomplicated ileus. After much complications as volvulus, gangrene, and peritonitis, the classic signs of obstructive ileus with dilated loops of bowel and fluid levels appear. Clinical evidence of ileus plus dilated loops of small bowel without fluid levels on the upright roentgenogram of the newborn warrant the diagnosis of uncomplicated meconium ileus.

Zeitschrift für Kinderheilkunde, Berlin

77, No. 5, 1956

* The Evaluation of Intellectual Capacities in the Ill Child. H. Harbauer.—p. 483.
Racial and Geographic Influences upon Serum Phosphatase in Childhood. R. Tascher and N. Muller.—p. 497.
Developmental Genesis of "Status Bonnevie-Ullrich": Developmental Mechanisms in Human Teratogenesis, Demonstrated on a Case of Status Bonnevie-Ullrich with Partial Absence of the Rhinencephalon. J. Freund.—p. 504.
Studies of the Fat Metabolism in Infancy: I. Balance Studies of Total Fat, Fatty Acids and Phosphatides in Infants with Parenteral Infection: A Contribution to the question of the Pathogenesis of Parenterally Caused Nutritional Disturbances in Infancy. W. Droese and H. Stolley.—p. 532.
The Volume of Reticulocytes: A Critical Discussion of a Paper by the Same Title by W. Kunzer, E. Ambs and D. Schneider (77:90). H. Weicker.—p. 544.
Studies of Spontaneous Oxydation of Hemoglobin from the Umbilical Cord and from Adults. K. E. Betke, E. Kleihauer, and M. Lipps.—p. 549.
Functional Maturation of Kidney Tubuli: Phenol Red Excretion in Infancy. U. Stave.—p. 554.
Electrophoretic Study of the Spinal Fluid in Childhood, Especially in Cases of Meningitis. G. Koch.—p. 563.
Hereditary Hamartomatosis (Peutz-Jeghers) (Melanin Spots on Skin and Mucosa with Intestinal Polyps). J. Brockhaus and H. Jochmus.—p. 577.
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Developmental Mechanisms of the Ehlers-Danlos syndrome: The Significance of a Central Focal Disturbance in the Genesis of Mesenchymal Dysplasias. J. Freund.—p. 611.
The Relationship of the Klippel-Trenaunay-Weber Syndrome to Localized Gigantism. H. Schonenberg.—p. 636.
The Temperature of Closed Incubators. J. Gleiss.—p. 653.
The Chemical and Colloidal Structure of the "Second Carbohydrate" (Polysaccharide) in Infant Nutrition. E. Huth.—p. 662.
A Peculiar, Hitherto Unknown Form of High Positioned Diaphragm. R. Pichlmayr.—p. 674.
* Electrophoretic Serum Protein Fractions in Clinically Evident Liver Damage in Childhood. W. Freislederer.
I. Primary liver diseases.—p. 680.
II. Secondary liver damage.—p. 705.

The Evaluation of Intellectual Capacities in the Ill Child.—Among 500 patients of an institution for emotionally disturbed children the author found 94 (19%) intellectually retarded children. He considered this figure as particularly impressive, since obvious cases of severe retardation or brain damage were not admitted. Twenty-eight children who at first gave the impression of defectiveness were discovered to have emotional disturbances caused by inner conflicts or environmental factors.

The difficulty of differentiating congenital from acquired defects by history, school reports, and psychological tests is pointed out. The differentiation of intelligence defects caused by organic damage due to illness from those caused by the environmental trauma of long hospitalization, such as in paralytic poliomyelitis or tuberculous meningitis, is of importance for the treatment and prognosis.

The management which is often left to specially trained teachers and the parents should include the constant active participation of a child psychiatrist in order to reorient the treatment according to the etiologic factors involved which often can be discovered only after prolonged observation. The placement of such children in the proper educational setting including vocational training in handicrafts and physical exercise is of great importance.

Electrophoretic Serum Protein Fractions in Clinically Evident Liver Damage in Childhood: I. Primary Liver Diseases; II. Secondary Liver Damage.—There were 849 serum electrophoretic determinations made on 334 children with mild and severe, primary and secondary liver damage.

Acute epidemic hepatitis and acute liver dystrophy cause a decrease in the albumins and increase in γ-globulin. α-globulin increase occurs as a result of inflammatory processes other than in the liver. β-globulin increase does not occur. Alterations in the γ-globulin levels are most reliable indicators for severity and stage of the disease. These changes are minimal in hepatitis in small infants. The electrophoretic pattern of liver cirrhosis and biliary atresia showed no characteristic changes.

Among the conditions causing secondary liver damage hemolytic jaundice was found to produce no changes, except for γ-globulin increases in cases associated with liver

enlargement. Similar findings were noted in erythroblastosis. Cardiac decompensation and rheumatic disease show no characteristic electrophoretic pattern. A γ-globulin rise occurs with decompensation or increased rheumatic activity. Liver enlargement in the course of infectious diseases or diabetes mellitus showed no consistent influence on the protein patterns. Blood diseases leading to hepatic enlargement show only γ-globulin increases, probably associated with or caused by changes of the reticuloendothelial system of the liver. No characteristic changes in the protein patterns in cases of drug intoxications could be observed.

In summary the author states that electrophoretic protein analysis is not helpful in the diagnosis of specific diseases but may give an indication of the severity and progress.

Miscellaneous

Acute Contagious Diseases

ON THE CLINICAL AFFINITY OF INFECTIOUS DISEASES. Polski tygodnik lek. 10:1078-1081, 1955.

The experimental biological tests, performed on animals by Pasteur, Nicolle, Ramon, Cole, Rivalier, Moro, established the theoretical foundations for phenomena encountered in the clinic of infestious diseases.

In view of a growing wave of scarlet fever and chickenpox the author considers himself justified to take up the long abandoned conceptions of scarlatina varicellosa (Pospischill, Weiss, Schlossmann, Port, Mitchell, Nobécourt, Hottinger). He has observed many cases of this disease which were a variety of the wound scarlet fever. The author describes the cases and discusses the differential diagnosis.

MIKULOWSKI.

Acute Infectious Diseases

SOME CASES OF SEPSIS OF THE URINARY TRACT IN INFANTS, TREATED BY TETRACYCLINE. G. COCOZZA and R. FEROLA, Pediatria 62:877 (Nov.) 1954.

Five girls between 8 and 11 months of age and sick with fever and pyuria due to gram-negative organisms, recovered rapidly after the giving of tetracycline (65 to 100 mg. daily in four divided doses). Several of these children had previously been given streptomycin or penicillin without any benefit.

HIGGINS, Boston.

SOIL AS A NATURAL RESERVOIR FOR HUMAN PATHOGENIC FUNGI. LIBERO AJELLO, Science 123:876 (May 18) 1956.

The author has made an extensive survey of soil samples collected in the United States, and to a lesser extent those from Canada, Peru, Hawaii, Panama, Venezula, and Nigeria. A total of 1215 samples were examined for pathogenic fungi; the largest single group (710) being obtained from Tennessee.

Microsporum gypseum was the fungus most frequently recovered, being found in 27% of the samples tested and with a wide geographical distribution. Histoplasma capsulatum was next in frequency (6.4%), being found in Central and South American soil as well as in Tennessee. When only those soil samples originating from chicken areas in Tennessee are considered, the percentage of recoveries rises to the high figure of 39%.

Occasional recoveries of such species as Cryptococcus neoformans, Coccidiodes immitis, Candida albicans, and Allescheria boydii are also reported.

FORBES, Rochester, N. Y.

FACTORS IN HUMAN MILK INTERFERING WITH INFLUENZA-VIRUS ACTIVITIES. R. K. SILVER, G. BRAUN, F. ZILLIKEN, G. H. WERNER, and P. GYÖRGY, Science 123:932 (May 25) 1956.

The authors have demonstrated that a certain fraction, as yet uncharacterized, of deproteinized human milk possesses hemagglutinin inhibitor activity when tested against one strain each of influenza-A and influenza-B virus.

The authors also note that copper, when present in amounts of 10-30 micrograms per milliliter, also possesses antiviral activity. In the studies reported above precautions were taken to remove copper from the milk samples.

FORBES, Rochester, N. Y.

VULVAL VACCINATION FROM CATHETERIZATION. G. CANESTRI, Lattante 26:475 (July) 1955.

A one-year-old girl was seen in a clinic in Alexandria, Egypt, with vaccinia of the vulva. She had been catheterized for pyuria in Novara, Italy, 15 days previously; the lesion had first been recognized 8 days previously.

This is another case to be added to the epidemic of 24 cases of like lesions occurring in children who had been catheterized in Novara and reported by Toscano and Angela in *Minerva Pediatrica* (5:987 [Nov. 15] 1953). It is of interest that the virus infection had been carried over a distance of several hundred miles during the incubation period and that the exact nature of the lesion might have been missed, if the account of the epidemic had not been published in a medical journal.

HIGGINS, Boston.

SPEECH DISORDERS RESULTING FROM BULBAR POLIOMYELITIS. D. E. MORLEY, J. Speech & Hearing Disorders 20:156:163 (June) 1955.

Bulbar poliomyelitis with chronic damage to the cranial nerve nuclei produces disturbances of mastication, swallowing, various paralyses of the face, tongue, and laryngeal muscles, with resulting articulation defects, hypernasality, and dysphonia. In some cases the loss of motor function was confined to the acute stage and followed by a degree of recovery. The speech therapist can provide a training program for chronically paralyzed cases consisting of activities to improve or restore oral motor skills. The amount of improvement is dependent on the extent of damage, the amount of natural recovery, the initiative and persistence of the patient, and the effectiveness of the therapy program.

PALMER, Wichita, Kan.

STAPHYLOCOCCIC PNEUMONOPATHY IN INFANTS. L. ROCCO and G. TOTTINI, Minerva pediat. 7:393 (March 24) 1955.

There is a high death rate in infants, and especially in the debilitated and very young, from staphylococcic pneumonia. It is especially prone to occur in epidemics among the newborn infants in hospitals. The pneumonia is often secondary to staphylococcic infections elsewhere on the body. The organisms may enter the lungs through the air passages or through the blood stream.

The early stages of staphylococcic pneumonia are toxic while the later stages are characterized by mechanical restriction of the respiration. Sequellae to the initial pneumonitis may be lung abscesses, pleuritis and empyema, bullous pneumonia, and pneumothorax. Surgical procedures may be necessary, when mechanical damage threatens the patient's life. The critical stage of the illness is usually passed by the end of the second week, and then the prognosis becomes better in that further complications are unlikely.

Antibacterial drugs and antibiotics are the main basis of treatment; they may, or should, be alternated in order to circumvent germ resistance. The following table shows results of tests as to the sensitivity and resistance to antibiotics of cultures of Staphylococcus aureus from cases of pulmonary involvement.

DRUG	TESTS	SENSITIVE	RESISTANT
Streptomycin	16	9	7
Penicillin	16	1	15
Streptomycin	16	9	9
Chloramphenicol	16	15	1
Aureomycin	16	14	2
Terramycin	16	12	4
Erythromycin	7	6	1

HIGGINS, Boston.

ON THE SIGNIFICANCE OF THE COLLOIDAL LABILITY OF THE SERUM IN LEISHMANIASIS AS RELATED TO THE DYSPROTEINEMIA AND BONE MARROW FINDINGS. G. MURANO, Pediatria 63:207 (March) 1955.

Four cases of kala-azar in children are reported, especial attention being directed to the electrophoretic study of the serum proteins, the Boselli test for gamma globulin, and the albumin:globulin ratio. The results of these tests paralleled and even may be used in place of blood morphological and liver function tests.

HIGGINS, Boston.

THREE CASES OF PARAINFECTIOUS ENCEPHALITIS RELIEVED BY ACTH. G. CROCCO and G. DI GRUTTOLA, Pediatria 63:284 (March) 1955.

Three children, 12 to 15 months of age, were given 15 mg. ACTH every 6 hours, in addition to antibiotics, on the premise that the condition was allergic in nature. The convulsions and encephalitic symptoms were quickly relieved in two cases, but the treatment was of no benefit in the third case, probably because it was started late.

HIGGINS, Boston.

THE ORAL USE OF PENICILLIN AND SULPHAMIDES IN PEDIATRICS. A. VIANELLO and A. M. CASAVOLA, Pediatria 63:271 (March) 1955.

Oral medication consisting of 300,000 to 400,000 Units penicillin and 1.5 to 2 gm. of a mixture of sulfonamide drugs was given daily to a group of 35 children, some normal and

others with pneumonia, bronchitis, otitis, or tonsillitis. The medication was well tolerated and efficacious in relieving the infectious processes. A study of the feces revealed that there was a tendency for the percentage of Gram-positive bacteria to be diminished. There were no symptoms of gastrointestinal disturbances however.

HIGGINS, Boston.

THE TREATMENT OF PERTUSSIS BY ACTH, WITH FREQUENT RADIOLOGICAL CHECKS. G. DI GRUTTOLA and U. DE BELLIS, Pediatria 63:73 (Jan.) 1955.

Fifteen children with pertussis were given treatments by intradermal injections of 3.5 to 16 mg. ACTH daily over a period of 5 to 13 days. The cyanosis and vomiting usually were relieved after three to four days and the paroxysmal coughing after six days. Frequent x-ray chest films were taken, several of which are depicted in the article. The pulmonary changes on the x-ray film were observed to disappear at the same time that the clinical findings and the blood counts became normal.

HIGGINS, Boston

THE INCIDENCE OF SALMONELLA INFECTIONS IN CASES OF GASTRO-ENTERITIS IN CHILDREN. A. VECE, Pediatria 62:932 (Nov.) 1954.

From a group of 45 infants and small children with gastroenteritis in a children's hospital in Naples, stool cultures were positive for Eberthus typhosus in 3 cases, for paratyphoid-B organisms in 11 cases, for other salmonella organisms in 4 cases, and for Shigella organisms in no cases.

HIGGINS, Boston

ANOTHER WORD FOR SUBCUTANEOUS SMALLPOX VACCINATION. F. HAMBURGER, M. KAISER, A. REUSS, and H. ZISCHINSKY, Wien. klin. Wchnschr. 67:666 (Sept. 2) 1955.

Reasons for the preference of subcutaneous as against the percutaneous smallpox vaccination are given.

AMBERG, Rochester, Minn.

CARDIAC INVOLVEMENT IN POLIOMYELITIS. G. SCHAPER and B. S. SCHULTZE-JENA, Ztschr. Kinderh. 76:91, 1955.

During the 1952 epidemic, electrocardiographic changes could be demonstrated in 28 out of 54 children with poliomyelitis. The authors considered as causes direct action of the virus upon the cardiac muscle, and pulmonary, metabolic, and central nervous system complications.

Changes resembling a beginning interstitial myocarditis could be demonstrated in three out of four cases in whom the heart muscle was examined histologically.

GLASER, Baltimore.

BLOOD LEVELS FROM ORALLY ADMINISTERED PENICILLINS G AND V RELATION TO FOOD INTAKE. WILFRED F. JONES JR. and MAXWELL FINLAND, New England J. Medicine 253:754-761 (Nov. 3) 1955.

Penicillin V is now available to pediatricians. This type of penicillin differs from penicillin G by a single oxygen molecule, but is markedly different in its physical properties.

The authors demonstrate that penicillin V also differs in its absorption and activity against some susceptible bacteria.

Their findings suggest that penicillin V should be more active than penicillin G when given by mouth both in the prophylaxis and in the treatment of infections with the hemolytic Streptococcus. Their preliminary work indicates that useful levels may be sustained during oral administration of penicillin V at intervals of four hours.

Further work with orally administered penicillin V in other susceptible infections is indicated.

WHEELOCK, Washington, D. C.

THE POSSIBILITY OF PREVENTING PERTUSSIS BY GIVING ISONIAZIDE. S. NASSO, Minerva pediat. 7:79 (Jan. 27) 1955.

In an institutionalized group of 60 under par children, 6 children developed pertussis and were isolated as soon as the diagnosis was made. As a prophylactic measure, the other children were given isoniazide in doses of 8 to 10 mg. per kilogram daily for 40 days. On the second day, one child was diagnosed as having pertussis and was isolated. None of the other children came down with pertussis, although several did contract colds. This prophylactic procedure

was suggested by a report by Rapisardi and Miane as to the therapeutic value of isoniazide in cases of pertussis (Abstract A. M. A. Am. J. Dis. Child. for June, 1954).

HIGGINS, Boston.

AN EPIDEMIC OF SALMONELLA INFECTION (TYPE NEWPORT) IN CHILDREN. HUGO FRITSCH, Monatsschr. Kinderh. 103:339-342 (July) 1955.

An epidemic outbreak of salmonellosis due to type Newport occurred in a German children's hospital and affected 34 children ranging in age from 16 days to 6 years. Organisms were isolated from the stools of all patients. It was difficult to evaluate the efficacy of antibiotic treatment used; however, eradication of the organisms from the stool was not affected by it. Stool cultures remained positive for several months in the great majority. Focus of the infection was found to have been a diaper-rinsing machine and spread of the infection occurred by contact with diapers.

HARTENSTEIN, Syracuse, N. Y.

Chronic Infectious Diseases

THE FIBRINOLYTIC ACTIVITY OF THE PLASMA IN EARLY PRIMARY TUBERCULOSIS. A. DEL PRINCIPE and M. C. SOLERI, Pediatria 62:870 (Nov.) 1954.

The fibrinolytic activity of the blood plasma of a group of children in various stages of primary tuberculosis was determined by the method of Cervini and Ficola. The more active the tuberculous process, the lower the fibrinolytic activity. A constant ratio was found to exist between the fibrinolytic activity and the red-cell sedimentation time. The opinion is expressed that the fibrinolytic activity is an even better index of tuberculous activity than is the sedimentation rate.

HIGGINS, Boston.

CHROMONEUROSCOPY MODO FLATAU IN THE TREATMENT WITH STREPTOMYCINE OF TUBERCULOUS MENINGITIS IN CHILDREN. Polski typodnik lek. 10:216-220, 1955.

In 100 children with tuberculous meningitis treated with streptomycin (partially also with isoniazid) there was performed the chromoneuroscopic Flatau's reaction in the cerebrospinal liquid. In 60 cases the reaction was positive, in 40% negative. The reaction was positive in average up to the eighth week of the treatment with average pleocytosis amounting to 188 cells in 1 cu. mm., the protein level being 104 mg. per 100 cc., sugar level 32 mg. per 100 cc., chlorides 653 mg. per 100 cc. The chromoneuroscopic Flatau's reaction was negative on the average in the 20th week of the treatment with pleocytosis amounting to 31 cells, the protein level 23 mg. per 100 cc., sugar 53 mg. per 100 cc., chlorides 708 mg. per 100 cc. The chromoneuroscopic reaction corresponds on the whole to the most typical indexes of biological activity of the tuberculous process in the course of tuberculosis meningitis and may also prove helpful in establishing the prognosis and in therapeutical indications for applying antibiotics.

MIKULOWSKI.

A PSYCHOLOGICAL EVALUATION OF CHILDREN, WHO HAD BEEN CURED OF TUBERCULOUS MENINGITIS. M. CARTA and A. PACI, Minerva pediat. 7:1257 (Oct. 13) 1955.

Intelligence quotients by the Terman-Merrill test were determined on 18 children one to five years after their recovery from tuberculous meningitis. The I. Q. on one child was 1.10, in three 1.00, in seven 0.90 to 0.99, in four 0.80 to 0.89, and in three 0.70 to 0.79. Some of the children showed emotional lability, being very conscious as to their health and having a tendency to be self-centered and with an inferiority complex. The children with the higher I. Q. tended to be much more stabile emotionally.

HIGGINS, Boston

TUBERCULIN TESTING PROGRAM PRECEDING B. C. G. IMMUNIZATION. T. BAUMANN, Ztschr. Kinderh. 76:392, 1955.

The Moro patch test was considered the most reliable and suitable (100% reliability in positive cases in the first 10 years of life and no untoward reactions).

Of a rural slightly industrialized population of 30,000 in Switzerland, 11.6% showed positive reactions at 7 years, 33% at 16 years, 61% at 25 years, and 91% at 55 years of age. Compared with earlier studies this constitutes a considerable improvement.

The negative patch test in children under 10 years was followed by BCG immunization; when negative in persons above 10 years Mantoux test (10 T.U. of PPD Tuberculin Berna) was applied and if negative, BCG was given.

The author opposed the use of the oral immunization method because of the danger of a "second Lübeck" accident. He also feels that the loss of a diagnostic tool due to immunization is not a valid argument against such a program.

GLASER, Baltimore.

SOME CLINICAL ASPECTS OF ASCARIDIASIS IN CHILDREN. E. SEGNAGNI, Minerva pediat. 7:1172 (Sept. 29) 1955.

Three cases of massive infestation of Ascaris lumbricoides in children 2½ and 3½ years old are reported. As many as 151, 329, and over 600 round worms by count were recovered from these children. Each of the children had a partial intestinal obstruction, but relief was obtained without surgery being necessary. Abdominal palpation and x-ray films revealed sections of bowel distended by the parasites. Each case has to be handled on an individual basis. Many reports are listed from the literature of similar emergent and bizarre cases. In these cases, the anthelmintic used was castor oil and chloroform. One of the children developed a progressive pneumonitis with marked consolidation of the right lower lobe due to the parasites entering the lung; surgery was advised but refused; the child was released from the clinic against advice.

HIGGINS, Boston.

DISCREPANCY BETWEEN THE FREQUENCY OF MATERNAL TOXOPLASMA INFECTIONS AND THE NUMBER OF CONGENITAL TOXOPLASMOSIS STATISTICAL AND CASUISTIC CONSIDERATIONS OF CONATAL OLIGOSYMPTOMATIC TOXOPLASMOSIS. O. THALHAMMER, Wien. klin. Wchnschr. 67:697 (Sept. 2) 1955.

It is emphasized that every congenital brain injury might be due to toxoplasmosis.

AMBERG, Rochester, Minn.

Diseases of Blood, Heart and Blood Vessels, and Spleen

DEXTROCARDIA WITH SITUS INVERSUS AND CONGENITAL ATRIO-VENTRICULAR BLOCK. M. AMATO and A. COLLETTA, Pediatria 63:97 (Jan.) 1955.

A 4½-year-old boy had a situs inversus and an auriculo-ventricular block. The auricular beat was 115 and the ventricular 50. The child has not as yet had any clinical incapacity as a result of the block. The heart is of normal size.

HIGGINS, Boston.

TWO CASES OF INHERITED FAMILIAL TELANGIO-THROMBOPATHY. A. CAMERA and A. ROMAGNOLI, Pediatria 63:105 (Jan.) 1955.

Two brothers, 3 years and 16 months of age, respectively, showed marked vascular and capillary fragility and purpura. The number of platelets in each case was normal, but their function was definitely impaired. They were subject to frequent hemorrhages. The older boy's condition was ameliorated after transfusion, but two weeks later a severe epistaxis marked the beginning of a rapid downhill course and fatal ending. The younger boy's bleeding was never so severe and has thus far been easily kept under control.

HIGGINS, Boston

THE BLOOD SUGAR CURVE FOLLOWING THE FEEDING OF SUGAR TO INFANTS WITH PERNICIOSIFORM ANEMIA. F. LO JACONO, Pediatria 63:45 (Jan.) 1955.

When five infants and children with a pernicious-like anemia were given a sugar tolerance test, the blood sugar curves were essentially normal; one other similar child showed a definitely flat curve, however, and two others somewhat flattened curves. When these three children had had a course of treatment with vitamin B_{12} and liver extract, their sugar tolerance curves approached those of normal children.

HIGGINS, Boston

DREPANOCYTEMIC ANEMIA. G. LOMBARDO, Pediatria 63:230 (March) 1955.

A 12-year-old girl presented the findings of a severe hemolytic anemia with febrile episodes, arthritic pains and a marked splenohepatomegaly. A diagnosis of sickle-cell anemia was only

made when a smear of fresh blood revealed the sickle cells. A sister had died at the age of 4 years of diphtheria, but she also had had anemia and rheumatic pains. The bloods of both parents and a younger brother showed sickling of the red cells, but they were not anemic.

HIGGINS, Boston

THE ELIMINATION OF FATS IN THE PERNICIOSIFORM ANEMIA OF INFANTS. F. LO JACONO, Pediatria 63:260 (March) 1955.

The percentage of fat eliminated in the stools of infants with perniciosiform anemia averaged 23.8% of the intake, as compared with 10% in the stools of normal infants. This steatorrhea diminished rapidly after the giving of vitamin B_{12} orally and of liver extract parenterally. The relief of the steatorrhea was much more rapid than in cases of sprue.

HIGGINS, Boston

ACUTE ERYTHREMIA: ITS HISTOGENESIS AND ITS RELATION TO ERYTHRO-LEUKEMIA. A. GENTILI and M. LOPEZ, Pediatria 63:161 (March) 1955.

The case of a female infant, who died at the age of 6 months after a 4½-months illness, is presented. A sister had died at the age of 10 months of a blood disease, diagnosed as erythroleukemia, and optic atrophy. On admission to the hospital at the age of 54 days it was found that she had enlarged liver and spleen and an anemia. The Hb. was 49%, the RBC 2,480,000, nucleated cells 61,550, of which 39,060 were erythroblasts. Erythrobastic cells predominated on the bone-marrow smears. At postmortem examination, the child appeared dystrophic and anemic. There were diffuse hyperplasia of the marrow and focal areas of hematopoiesis in the kidneys and meninges.

HIGGINS, Boston

ACUTE MYELOID LEUKEMIA FOLLOWING PROLONGED $IODINE^{131}$ THERAPY FOR METASTATIC CARCINOMA, S. M. SEIDLIN, E. SIEGEL, A. A. YALOW, and S. MELAMED, Science 123:800 (May 4) 1956.

Two adult patients are reported. The first received 1455 mc. of $iodine^{131}$ over a period of four years because of a metastatic thyroid carcinoma. Fatal leukemia developed at the end of this period. The second patient received a total of 1730 mc. over a five-year period. The estimated cumulative blood radiation dose was 600 and 550 r for the two patients, respectively, which is of course greatly in excess of that sustained by the usual patient under treatment for hyperthyroidism.

FORBES, Rochester, N. Y.

HISTOGENESIS AND HEMOPOIESIS OF THE THYMUS IN THE HUMAN FETUS: A CYTOLOGICAL STUDY BY THE APPOSITION METHOD. S. AURICCHIO and F. BRESCIANI, Pediatria 62:833 (Nov.) 1954.

The thymus glands of 31 fetuses of various ages were studied histologically in an endeavor to gather information as to the histogenesis of the thymus gland. The conclusion was reached that the thymus is the first site where lymphocytes are formed.

HIGGINS, Boston

RADIOACTIVE FALLOUT AND RADIOACTIVE STRONTIUM. W. F. LIBBY, Science 123:657 (April 20) 1956.

The author, a member of the U. S. Atomic Energy Commission, discusses certain hazards of the atomic bomb.

The magnitude of the fallout depends on the type of burst, whether in air or on the surface of the ground, and in the latter case on the nature of the underlying soil.

Essentially the radioactivities resulting from a bomb burst can be separated into two categories: (1) those induced in the environment by the action of escaping neutrons. The principal effect here is the production of radioactive carbon (C^{14}); the author concludes that the amount of C^{14} produced is so small as to constitute a negligible hazard; (2) those products dependent on the nature of the weapon itself. Some 90 different fission products are formed, and of these radioactive strontium (Sr^{90}) constitutes 4%-5% of the total.

Sr^{90} is important for several reasons: it has a long half-life (28 years); it is a bone-seeker and once deposited tends to remain in the body for a long time, and the probability of ingestion by human beings is high. Strontium is deposited in plants, bodies of water, and soil. However, it is of some interest that the strontium content of milk and cheese is only

about 1/5 to 1/10 that which would be predicted from the content of the grass eaten by the cow. To date the rediostrontium of human bodies is the lowest of all animals so far measured. Despite all of the factors mentioned above, the total uptake of Sr^{90} by man at present corresponds to about 1/1000 of the maximum permissible dose.

Various forms of fallout are described. After a full discussion of the local hazards of fallout, the author concludes that world-wide hazards from the present rate of bomb testing are insignificant.

FORBES, Rochester, N. Y.

THE MUCOPROTEINS IN RHEUMATIC DISEASE. B. FANTUZZI and C. NEUHAUS, Minerva pediat. 7:478 (April 14) 1955.

The mucoprotein content of the sera of normal children was found to approximate 6 mg. per 100 cc. (maximum 7.8 mg. per 100 cc.), and of children with active rheumatic disease 12.2 mg. per 100 cc. before and 8.6 mg. per 100 cc. after effective therapy. The plotted curves of the mucoprotein serum content were found to parallel the curves of the red cell sedimentation rate. Therefore, the determining of the mucoprotein content is acclaimed as of great diagnostic and prognostic value. The method of Winzler (*J. Clin. Invest.* 27:609, 1948) was used in these studies.

HIGGINS, Boston

FURTHER IN VITRO AND IN VIVO STUDIES AS TO THE EFFECTS OF PENICILLIN AND OF STREPTOMYCIN IN THE BLOOD COAGULATION OF CHILDREN. E. SEGNANI and E. ARDITI, Minerva pediat. 7:379 (March 24) 1955.

Both penicillin and streptomycin have a heparin-like action on the blood of children, i.e., in small concentrations they increase the tendency of the blood to coagulate, and in high concentrations they reduce it. When tests were made in vivo, it was found that the usual blood concentrations of these two drugs did not lower appreciably the tendency of the blood to coagulate. It is apparent that only a prolonged and heavy dosage of these drugs could lead to hemorrhagic conditions such as purpura or bleeding.

HIGGINS, Boston

COOLEY'S ANEMIA IN AN ADULT. G. SANSONE and L. NOCETO, Minerva pediat. 7:1154 (Sept. 29) 1955.

A case of Cooley's anemia in a boy of 16 years from Sardinia is presented. The case had been diagnosed as a hemolytic anemia when he was 4 years old. Both parents had the thalassemic trait; two brothers were apparently normal. The boy had an oriental facies, was physically dwarfed and sexually infantile; the bones of the skull and extemities showed the typical osteoporosis and moth-eaten appearance occurring in bones in that disease. The blood contained a high percentage of fetal hemoglobin; there was no erythroblastosis.

HIGGINS, Boston

DIAGNOSIS AND TREATMENT OF ORTHOSTATIC CIRCULATORY DISORDERS IN CHILDHOOD. E. CAPEK-SCHACHNER and W. SWOBODA, Wien. klin. Wchnschr. 67:678 (Sept. 2) 1955.

Sixteen patients 7-14 years of age with orthotic symptoms were treated with "Carnigen," an extract from organs of warm blooded animals containing nucleosides with constant adenosine combined with *p*-oxyphenyl methylamin propanol hydrochloride (Farbwerke Hoeschst A. G.). The children received t.i.d. as many drops as their years of age. This was increased when needed to as many as 15 drops t.i.d. The drug was given for a period of 6-8 weeks with gradual cessation of medication. In most of the cases a complete and lasting result was obtained.

AMBERG, Rochester, Minn.

DEXTROVERSION OR DEXTROTORSION OF THE HEART. E. ZDANSKY, Wien. klin. Wchnschr. 67:655 (Sept. 2) 1955.

For reasons given, the term dextrotorsion is preferred to dextroversion. It is a rotation of the heart to the right. Various forms of dextrotorsion are described and their x-ray pictures are discussed. Two cases are reported with associated anomalies of skeleton of the thorax, although these anomalies were not of causative significance. One of the two cases was a 57-year-old man, the other a 4-year-old boy, and neither had any cardiac symptoms.

AMBERG, Rochester, Minn.

CLINIC AND PATHOLOGY OF ESSENTIAL RETICULO-GRANULOMATOSES IN CHILDHOOD. H. RÖSSLER, Wien. klin. Wchnschr. 67:688 (Sept. 2) 1955.

A detailed report is given of a case of Letter-Siwe (or Abt.Letterer Siwe) disease in a boy 7 months of age and also of a case of a 2 7/12-month-old boy where the pathologist reported a generalized xanthomatous granuloma. The relationship of Hand-Schüller-Christian disease, Abt. Letterer Siwe disease, and eosinophile granuloma of bone is discussed.

AMBERG, Rochester, Minn.

CONGENITAL ABSENCE OF INTRAHEPATIC PORTAL VENOUS SYSTEM SIMULATING ECK FISTULA: REPORT OF A CASE WITH NECROPSY FINDINGS. GISELA HELLWEG, A. M. A. Arch. Path. 57:425 (May) 1954.

This is the only case of its type in a human being, known to the author to be reported in the literature, in which the terminal portion of the portal vein and of its intrahepatic branches were congenitally absent. The case is that of a 5½-month-old white girl born 3 to 4 weeks prematurely after an otherwise normal pregnancy. There was jaundice at birth, but it faded at one month of age. Slight cyanosis was noted at birth and gradually increased with the appearance of wheezing and coughing. Occasional vomiting began at 2 months of age, but in spite of this the infant continued to gain weight slowly. At the time of admission the infant was cyanotic, dyspneic, but active. An exploratory right thoracotomy was performed. Postoperatively, the respirations and pulse rates remained rapid, and the patient was cyanotic when out of oxygen. On the ninth postoperative day the infant became increasingly cyanotic, respirations noisy, and she died on the tenth postoperative day. At autopsy, the heart was greatly enlarged, ductus arteriosus and foramen ovale patent. There were pulmonary edema and congestion of viscera. The segment of the portal vein extending from its confluence with the coronary and splenic veins to the usual point of entry to the liver, as well as its entire intrahepatic distribution was absent. The usual tributaries of the portal vein drained into a large vessel which took its course directly cephalad along the posterior liver surface; it joined the hepatic vein at the superior liver edge. This vessel and the hepatic vein joined to form the supradiaphragmatic portion of the inferior vena cava which entered the right atrium normally. The subdiaphragmatic portion of the inferior vena cava was formed by the confluence of the right and left common iliac veins approximately at the level of the fifth lumbar vertebra. It was then joined by the renal veins. It passed through the diaphragm on the right lateral aspect of the thoracic vertebrae to join the enlarged azygos vein. This vessel then entered the right atrium in a normal position. The falciform ligament and the ligamentum teres were absent. The hepatic artery, normal in structure and caliber, was the only blood vessel entering the liver hilus, accompanying the hepatic bile ducts. The liver itself was relatively small (165 gm., normal 188 gm.) and was abnormally lobulated. On microscopic examination the heart showed numerous small infarcted zones with some calcium deposition. The lungs showed edema, pneumonitis, congestion, and marked increase in small, thickened arteries. The liver showed a distortion of the hepatic architecture with a marked variation in the size of the liver lobules. The periportal areas contained normally formed bile ducts and numerous coiled small branches of the hepatic artery. No intrahepatic branches of the portal vein were recognized. The liver cells throughout the sections contained small fat vacuoles. Small areas of necrosis were present in some central areas. The sinusoids in the intermediary and peripheral lobular zones were dilated. The microscopic sections of the remaining viscera were not remarkable. Death, explained by the author, was attributed to circulatory failure due to an increased cardiac output.

CHAN, San Francisco.

IRON AS TRACE ELEMENT IN MILK AND MILK MIXTURES. K. H. SCHÄFER, A. M. BREYER and H. KARTE, Ztschr. Kinderh. 76:501, 1955.

Practically all iron can be dissolved and separated with 6 N HCl. The iron level in human milk is higher than in cow's, sheep, or goat's milk but decreases considerably during the lactation period. Various cereal mixtures contain relatively high values of iron and therefore also the milk mixtures which contain such cereals. Some iron occurs in cream in a fat-bound form, and some is probably protein bound and occurs in the whey.

GLASER, Baltimore.

CONGENITAL ANGIOCARDIOPATHIES AND CONCURRENT MALFORMATIONS. W. HECK. Ztschr. Kinderh. 76:542, 1955.

A study of 300 children with congenital cardiac malformations revealed other malformations in 139 children.

The type, frequency, and familial occurrence of these anomalies is shown in five tables.

GLASER, Baltimore.

A CASE OF CHRONIC RETICULOENDOTHELIOSIS IN A CHILD OF THREE YEARS. Polski tygodnik lek. 10:483-485, 1955.

A country child was admitted to the hospital with history of enlargement of the abdomen lasting since one year, pallor, and nasal bleeding. On admittance a tumor of the liver and spleen, anemia, infantilismus, with deviation of growth amounting to 13.5% and of weight to 26% beneath normal, were found. The temperature was normal. Pirquet and Wassermann tests were negative, hemoglobin 50%, erythrocytes 2,660,000, leucocytes 3500, blood platelets 50,000, blood-cell resistance to the hypotonic salt solutions normal, bilirubin 2.13 mg. per 100 cc., the glycemic curve normal. Bone-marrow and glandular biopsy: reticuloendotheliosis. The child was treated successfully with ACTH and x-ray irradiation.

MIKULOWSKI.

A CASE OF STENOSIS OF VENA LIENALIS /WALLGRENS DISEASE/ IN A FOUR-YEAR-OLD BOY, TREATED BY OPERATION. Polski tygodnik lek. 11:372-374, 1956.

Clinical description of a case of stenosis of the vena lienalis in a 4-year-old boy together with the description of the operation (splenectomy). Two years observation after the operation showed a completely satisfactory condition of the child.

MIKULOWSKI.

Diseases of Nose, Throat, and Ear

THE SIGNIFICANCE OF EARLY ORTHODONTIA IN CLEFT PALATE HABILITATIVE PLANNING. J. DANIEL SUBTELNY, J. Speech & Hearing Disorders 20:135-147 (June) 1955.

Orthodontic anomalies and their early treatment in cleft palate are discussed. Early treatment is directed toward the counteraction of adverse muscular influences. Early establishment of more normal intermaxillary relationships frequently brings about an improvement in many associated conditions, such as ventilation, more normal growth, etc. Speech also develops more readily and rapidly on the basis of more normal structures. There is minor danger of the surgically united palate reopening. Several periods of treatment may be necessary, and long periods of retension are inevitable. Work with orally sensitized patients in these ages is extremely difficult.

PALMER, Wichita, Kan.

Diseases of Lungs, Pleura, and Mediastinum

EXPERIMENTAL ASPIRATION PNEUMONIA: III. PNEUMONIA PRODUCED BY INTRATRACHEAL INJECTION OF CARBOHYDRATE SOLUTIONS. ROSS H. SMITH and THOMAS J. MORAN, A. M. A. Arch. Path. 57:194 (March) 1954.

During experiments on the production of acute pulmonary edema in rabbits by intratracheal injection of milk, feeding mixtures, and sugar solutions, it was noted that animals surviving the initial injection of the material subsequently developed pneumonia. The pneumonia produced by injection of sugar solutions was similar in many respects to that produced by injection of milk or solid foods. The reactions to the injected sugar solutions included acute pneumonia with abscess formation and empyema and mononuclear pneumonia with chronic granulomatous reaction, fibrosis, collapse, and emphysema. The pneumonia is similar to, but usually not so severe as, that produced by injection of similar amounts of milk. The authors suggest that the practice of many pediatricians of substituting carbohydrate solutions for milk in the care of newborn infants with feeding problems would seem hazardous in view of the previously reported production of acute pulmonary edema in rabbits by intratracheal injection of strong carbohydrate solutions and the findings reported here of aspiration pneumonia caused by dilute sugar solutions.

CHAN, San Francisco.

ALEVAIRE AS A MUCOLYTIC AGENT. MAURICE L. TAINTER, FREDERICK C. NACHOD, and JOSEPH G. BIRD, New England J. Med. 253:764-67 (Nov. 3) 1955.

The authors discuss the rationale for the application of a detergent material to exudative tracheobronchial and pulmonary diseases.

The physicochemical forces involved are demonstrated by various experiments which are described.

The authors conclude that "Alevaire, as an aerosol, may be considered a true topically acting expectorant. It may also serve as a deeply penetrating surface-active vehicle for many drugs, including bronchodilators and antibiotics."

WHEELOCK, Washington, D. C.

ISCHEMIA OF ATELECTATIC AREAS OF THE LUNG AND ITS FUNCTIONAL RELATION TO VENTILATION AND BLOOD FLOW. R. BULGARELLI, Minerva pediat. 7:1149 (Sept. 29) 1955.

In evaluating the causes of areas of pulmonary atelectasis, one has to consider not only obstruction of the bronchus, but also pressure on the nerves and on the blood vessels of the lung. Each of the three tissues are subject to pressure from glands or scar tissue. For a more accurate diagnosis before any thoracic surgery is attempted, not only bronchoscopy and brochograms but also angiograms depicting the pulmonary arteries should be made. In this article a thorough study of a case of atelectasis in a boy with tuberculous exposure is presented with illustrations of the x-ray films obtained on angioscopy and bronchography.

HIGGINS, Boston.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

GASTRO-DUODENAL ULCER IN A CHILD. M. MORENO DE ORBE, Revista españ. pediat. 11:51-76 (Jan.-Feb.) 1955.

The author presents the case history of a boy of 10 years with a duodenal ulcer. He includes x-ray and other laboratory determinations as well as clinical details and photographs.

The operation was a gastric resection of the Billroth II type. This was necessary because of the stenosis and gall-bladder adhesions which had developed in the course of the disease.

The author reviews the literature and discusses diagnosis, treatment, etc. He also points out that children who develop ulcers are described as nervous and tense but not psychotic or even unstable.

ALLEN, Santa Fe, N. M.

"MELENA" NEONATORUM: THE SWALLOWED BLOOD SYNDROME. L. APT and W. S. DOWNEY, JR., J. Pediat. 47:6-12 (July) 1955.

The authors describe a test to distinguish between ingested maternal blood and infant's blood in red, grossly bloody stools of newborn infants. The test is not accurate with tarry stools.

The technique: Mix a small amount of red bloody stool with water (tap or distilled) in a test tube to lyse the erythrocytes and prepare a hemoglobin solution (one part stool to five or ten parts water). A distinct pink supernatant solution should result.

Centrifuge the test tube for one to two minutes at 2000 r. p. m. and then filter or decant the supernatant fluid.

To 5 ml. of this supernatant hemoglobin solution add 1 ml. of 0.25 N sodium hydroxide. Read in two minutes. Adult type hemoglobin (ingested blood) changes from pink to brown-yellow. Fetal hemoglobin (intestinal hemorrhage) remains predominantly pink. Peripheral blood of the infant who passed the bloody stool may be used in a control test.

The test is based on the fact that fetal hemoglobin is more resistant than adult hemoglobin to denaturation with alkali.

MACDONALD, Pittsburgh.

THE USE OF ANTIRETICULO-CYTOTOXIC SERUM IN ELEVEN CASES OF DYSTROPHY IN INFANTS AND YOUNG CHILDREN. F. COPELLO and G. VALLARINO, Pediatria 63:68 (Jan.) 1955.

Antireticulo-cytotoxic serum (SAC) is a proprietary preparation of the sera of rabbits and of goats which had received injections of extracts of human spleen and bone-marrow tissue. Eleven trophic children were given injections of SAC every three to five days. There were no untoward reactions to the treatments. Since each child gained weight, it appears that the serum acted as a stimulus to growth.

HIGGINS, Boston.

MELENA NEONATORUM. LEONARD APT, J. Pediat. 47:1-5 (July) 1955.

In an attempt to simulate ingestion of blood during delivery, Apt put blood into the stomachs of newborns by gavage tube. He was able to produce grossly bloody stools in this way for as long as 30 hours, and his gavaged infants showed occult blood in their stools (guaiac test) for as long as 87 hours after blood had been given.

This information may help the clinician who might otherwise assume that persistent grossly bloody stools and a positive chemical test for blood indicate continuing hemorrhage into the digestive tract of a newborn infant.

MACDONALD, Pittsburgh.

INFLUENCE OF AN EMULSIFYING AGENT (TWEEN 80) ON THE LIPEMIC CURVE OF DYSTROPIC INFANTS DURING DIGESTION. S. LI MOLI, Minerva pediat. 7:1181 (Sept. 29) 1955.

When 0.5 gm. of the emulsifying agent Tween 80 (Polysorbate 80 U. S. P., Sorlate, Abbot) was added to a formula feeding of 10 dystrophic infants, the peak of the lipemic curve was reached in the second hour after feeding, whereas without the polysorbate the peak was not reached until the third hour.

HIGGINS, Boston.

ORAL AND INTRAVENOUS METHODS OF CHOLECYSTOGRAPHY IN INFANTS. B. CARLETTI and L. PAPAGNI, Minerva pediat. 7:1241 (Oct. 13) 1955.

The gall bladder was visualized in 71% of healthy, in 50% of premature, and in 80% of dystrophic infants under 5 months of age when cholecystography was done by the intravenous method.

When the cholecystography was done by the oral method, visualization was obtained in none of the normal and in 47% of the premature infants under 5 months; visualization, however, was obtained in 50% of the normal infants 6 to 12 months old, in 80% of those 1 to 3 years old, and in all children over 3 years of age.

HIGGINS, Boston.

THE AMINO-ACIDEMIA CURVE IN CHILDREN WITH EPIDEMIC HEPATITIS FOLLOWING THE INTRAVENOUS INJECTION OF GLYCOCOLL. G. GROCCO and A. COLLETTA, Pediatrica 62:922 (Nov.) 1954.

An aminoacidemia curve is obtained by analyzing the blood sera obtained from fasting persons before and 15, 30, and 60 minutes after the intravenous injection of 0.015 gm. of glycocoll in a 12% solution. In the preicteric phase of hepatitis, a rise in the aminoacidemia was found in the 30-minute sample but had returned to fasting level at the 60-minute sample. In the acute phase of jaundice, the rise was more marked and was still present in the 60-minute sample. After recovery, no rise was found, and there was a marked fall in the curve in the 30-minute sample.

This procedure is recommended as the most sensitive of the tests for liver function.

HIGGINS, Boston.

Nervous Diseases

PERMANENT CENTRAL NERVOUS SYSTEM DAMAGE AND TOXICOSIS IN INFANTS (PRELIMINARY REPORT). N. HALLMAN, H. TÄHKÄ, and A. YLPPÖ, Ztschr. Kinderh. 76:413, 1955.

The Pediatric Department of the University of Helsinki conducted a follow-up study by questionnaire of 175 children aged 4 to 12 years who had suffered severe gastroenteritis and toxicosis in infancy. The study showed that of these children 6 were retarded and 13 had convulsions. In a control group of 171 children only 3 were retarded and 8 had convulsions. The possibility of lasting damage to the central nervous system due to toxicosis (severe gastroenteritis with toxic symptoms) is considered by the authors.

GLASER, Baltimore.

CASE REPORT OF A NEUROBLASTOMA SYMPATHICUM. HERBERT GROSS, Wein. klin. Wchnschr. 67:681 (Sept. 2) 1955.

The report concerns an infant which died after an exploration for an abdominal tumor which was diagnosed histologically as sympathogonioma arising from the abdominal sympathetic nerves.

AMBERG, Rochester, Minn.

AGENESIS OF THE SEPTUM PELLICIDUM, ASSOCIATED WITH SPINA BIFIDA CRANIAL LACUNAE, AND OTHER MALFORMATIONS. P. DURAND and C. ZUNIN, Minerva pediat. 7:1249 (Oct. 13) 1955.

The cases of three infants (3 days, 3 months, and 2½ years of age) with a congenital agenesis of the septum pellucidum are reported; the defect was detected by autopsy in one case and by pneumoencephalograms in the other two cases. The septum pellucidum is the brain tissue separating the two lateral ventricles of the cerebrum. This defect was accompanied by other congenital defects in at least two of the cases; they were club feet (two), cranial bone defect (two), mental retardation, hydrocephalus (two), spina bifida (two), sclerosis, finger abnormalities. The father of one child and cousins of another had spina bifida; thus it seems likely that this clinical syndrome has a hereditary basis.

HIGGINS, Boston.

THE USE OF MEGAPHEN IN THE PREPARATION OF CHILDREN FOR PNEUMOENCEPHALOGRAPHY. KARL-HEINZ BLECKMAN and DORA SALUS, Monatsschr. Kinderh. 103:337-338 (July) 1955.

Megaphen (Bayer, Leverkusen), a phenothiazine derivative, exhibits sympatholytic, vagolytic, spasmolytic, and sedative properties. Therefore, it was considered to be an agent to be tried prior to pneumoencephalography, a procedure involving stimulation of the vegetative nervous system. Tendency to collapse, increase in body temperature, leukocytosis, and blood pressure lability are often noted with this procedure.

Megaphen was administered to 20 children, ranging in ages between 13 months and 10½ years, who were suspected of having organic brain damage, prior to pneumoencephalography. Dosage was 1-2 mg/kg. by intramuscular route. Effects were noted after 15 to 20 minutes.

It was found that Megaphen without addition of a sedative did not produce enough relaxation for the performance of the procedure in the majority of cases. Blood sugar and white blood cell counts were performed in 13 patients and showed increases in all for both. Vasolability and tendency toward convulsions were not prevented. Recovery was rapid, especially in older children.

An additional seven patients received chloral hydrate or phenobarbital in addition to Megaphen. Marked advantages of these combinations were noted only in the older children.

HARTENSTEIN, Syracuse, N. Y.

MARKED KETONURIA IN CHILDREN DUE TO CRANIAL TRAUMA. G. CANESTRI, Pediatria 62: 913 (Nov.) 1954.

Ten children, 2 to 12 years old, showed ketonuria following severe trauma to the head from falls, blows, or automobile accidents. Vomiting had occurred in most but not all of the cases. In discussing a possible basis for the ketonuria, the following comments are made. Ketonemia may result from massive production of ketone bodies or from imperfect ketolysis. The liver is the main site for the production of ketone bodies. Hyperinsulinism will prevent glycogenolysis and hence indirectly lead to ketolysis. Hypophyseal extract will cause ketogenesis in animals, except in those which have been hepatectomized. Cerebral trauma acts on the adrenal gland, either through the nervous system or the pituitary gland, and by this means may cause ketosis through the liver.

HIGGINS, Boston.

Psychology and Psychiatry

"WHIRLING" BEHAVIOR IN DOGS AS RELATED TO EARLY EXPERIENCE. W. R. THOMPSON, R. MELZACK, and T. H. SCOTT, Science 123:939 (May 25) 1956.

An interesting experiment bearing on recent observations made on emotionally deprived young human infants has been carried out in dogs.

Scottish Terrier puppies were reared in isolation cages from the age of 1 to 8 or 10 months. No perception of outside environment was permitted. Eight of the eleven animals so treated developed abnormalities in activity and behavior, the most striking of these being attacks of "whirling." These attacks were characterized by jerky running in tight circles, agonized yelping, barking and snarling, and tail biting. None of the litter mate controls were afflicted.

The authors conclude that this bizarre behavior is dependent for its development on the conditions of restriction imposed in early life.

FORBES, Rochester, N. Y.

CHILDREN IN HOSPITALS. A. WALLGREN, Ztschr. Kinderh. 76:417, 1955.

Children are being treated in hospitals with increasing frequency. In the course of the last century progress has been made in nutrition and prevention of cross infection in hospitals. The same measures which prevented cross infection, however, produced emotional hospitalism, a subject of discussion at an international conference in Stockholm, Sweden.

A description of the various behavioristic reactions of the children to hospitalization, operations, separation from the mother, etc., is followed by suggestions for amelioration of the traumatic experience to the child. Honest explanations of what the child has to expect and why, and free expression and acceptance of the child's feelings are a prerequisite. In small children presence of the mother in the hospital, avoidance of not absolutely necessary painful procedures and introduction of anesthesia in a manner which will not produce fear are recommended. The child's own toys give him a feeling of contact with his home. Staff, personnel, and students are trained for their contact with parents and children, and close cooperation exists with the child psychiatrist and psychologist.

GLASER, Baltimore.

CERTAIN GOALS IN THE FIRST SESSION IN THE PSYCHO-THERAPY OF CHILDREN. J. PERTEJO, Rev. Españ. Pediat. 11:83-92 (Jan.-Feb.) 1955.

The author discusses certain necessary concomitants in psychotherapy in children. She points out that several sessions may be necessary to establish rapport with a child and that the absolute necessity for work with the parent precede treatment and continue for some time. The parents must have some understanding of what is being attempted.

She discussed one case in some detail in which the mother rejected the child because of frequent serious illnesses but by over-protection increased the child's dependence and immaturity.

ALLEN, Santa Fe., N. M.

Diseases of Genitourinary Tract

PSEUDOHERMAPHRODITISMUS MASCULINUS. RICHARD WAGNER, Wien. klin. Wchnschr. 67:659 (Sept. 2) 1955.

A 3-year-old child was operated upon for a left-sided inguinal hernia. The child had been regarded as female. At time of operation a prepuberal testicle was found and another in the right inguinal canal. External genitalia showed normal labia and a somewhat enlarged clitoris. A rudimentary vagina was present. Intravenous pyelogram revealed a reduplication of left renal pelvis and ureter. It is assumed that in spite of male genetics the development will proceed along feminine lines. It is not likely that a primary hormonal disturbance is responsible but a lack of sensitivity of the tissues to the male sexual hormone probably reaching back into fetal life. The 24-hour urine contained 3.3 mouse units of follicle stimulating hormones. The excretion of 17 ketosteroids was within normal limits. Sections of the skin were taken but could not be examined for sex chromosomes on account of improper preparation.

AMBERG, Rochester, Minn.

MODERN PROCEDURES FOR REMEDYING URETHRAL MALFORMATIONS SURGICALLY. A. SOSTEGNI and R. ASCOLI, Minerva Pediat. 6:978 (Dec.) 1954.

A well-illustrated article demonstrates a plastic surgical procedure for remedying the defect in cases of hypospedias.

HIGGINS, Boston.

RENAL ACIDOSIS. THE KIDNEY REACTION TO VARYING DOSES OF 2 ACETYL-AMINO-1,3,4 THIODIAZOL-5-SULFONAMIDE (DIAMOX). P. DURAND, F. CUSMANO, R. BRUNI, E. SORARU, B. DE MARCO, and A. BARBIERI, Minerva pediat. 7:467 (April 4) 1955.

The effect of giving to a group of children doses of the diuretic Diamox was at first the production of a mild acidosis with the lowering of the alkali reserve of the blood and the excretion of an alkaline urine containing considerable bicarbonate. After two days of such medication, the urine became neutral and the alkali reserve stabilized at its lower level. The pharmacological effect of the drug is ascribed to the inactivation of carbonic anhydrase; if large or frequent doses of Diamox are given, this inactivation is no longer apparent.

HIGGINS, Boston.

A Case of Masculine Pseudo Hermaphroditism in a Three-Year-Old Child. E. Comolli and B. Carletti, Minerva pediat. 7:1167 (Sept. 29) 1955.

A 3-year-old child presented the external genitalia of the female; a closer study revealed a nut-like body, which by biopsy proved to be a testis. Delay of any radical treatment seemed the wiser course to pursue until the child was older.

Higgins, Boston.

Diseases of Ductless Glands; Endocrinology

The Effects of ACTH on Glycemia and the Results of Glucose Tolerance Tests. E. Arditi, Minerva pediat. 7:373 (March 24) 1955.

The percentage of sugar in the bloods of eight children fell and in three children rose after a single injection of ACTH. A comparison of the blood sugar curves from glucose tolerance tests made before and after ACTH had been given for four days revealed more uniform curves when the ACTH had been given. The curves after the ACTH injections were always within limits accepted as normal; in no cases was there any glycosuria.

Higgins, Boston.

Advances in the Diagnosis of the Altered States of Adrenocortical Function. John C. Laidlaw, William J. Reddy, Dalton Jenkins, Najib Abu Haydar, Albert E. Renold, and George W. Thorn, New England, J. Med. 253:747-53 (Nov. 3) 1955.

Pediatricians must become more and more aware of the possibilities and variations of endocrine disease involving infants and children. In all cases of adrenocortical disease, for example, the final diagnosis will be made on the basis of all the information obtained from an accurate history and physical examination, appropriate x-rays, and laboratory studies.

The development of simple methods for the measurement of blood and urinary 17-hydroxycorticoids has facilitated the estimation of the quantity of hydrocortisone secreted by the human adrenal cortex. The availability of ACTH has opened the way to the exploration of adrenocortical reserve in a wide variety of physiologic and pathologic states. It now appears that the intravenous administration of ACTH with the determination of 17-hydroxycorticoids and 17-ketosteroids in blood or urine provides the most accurate means of quantitating adrenocortical response. Finally, the large-scale preparation of cortisone, hydrocortisone, and, more particularly, a highly potent derivative, 9-α-fluorohydrocortisone, has provided substances capable of inhibiting ACTH secretion. The study of urinary 17-hydroxycorticoids after fluorohydrocortisone administration and of the urinary 17-ketosteroids after the administration of all three compounds has made it possible to determine the degree of dependency of the adrenal cortex on the anterior pituitary gland in states of adrenal dysfunction in man.

Wheelock, Washington, D. C.

The Distribution of zinc-65 in the Rat Pancreas. Robert J. McIsaac, Endocrinology 57:571-579 (Nov.) 1955.

It is well known that zinc facilitates the crystallization of insulin and tends to prolong its biological action when present in suitable concentration. Although the pancreas appears to be involved directly in zinc metabolism, little is known concerning the role of the metal in the various tissues of this organ.

Zinc-65 entered both islet and acinar tissue, but the rates of loss from these two tissues were very strikingly different. Although the acinar cells lost the radioisotope quickly, the concentration in islet cells remained high and constant throughout the 92 hours of observation.

Jacobsen, Buffalo.

A Comparison of the Action of Human and Rat Liver Slices on Several Corticosteroids. Gerald M. Reaven, Endocrinology 57:580-587 (Nov.) 1955.

Recent studies have demonstrated the great capacity of the rat liver to metabolize adrenal cortical steroids, and, in so doing, to decrease their biological activity. In these experiments the author decided to compare the hepatic metabolism of aldosterone with other adrenal cortical steroids by incubating them with rat and human liver slices.

There are uniform differences in the rate of metabolism of adrenal cortical steroids by

human and rat liver. Of the steroids tested, desoxycorticosterone was the most sensitive, hydrocortisone the most resistant, and aldosterone and corticosterone were intermediate. The possible role of the liver in controlling the circulating level of steroids was discussed.

JACOBSEN, Buffalo.

ENDOCRINE RELATIONSHIPS IN MALES OF A RELATIVELY INFERTILE STRAIN OF WHITE LEGHORN FOWLS. K. GOODWIN, R. K. COLE, F. B. HUTT, and B. A. RASMUSEN, Endocrinology 57:519-526 (Nov.) 1955.

Among young males from two strains of White Leghorns differing in fertility, it was found that, while the growth of the body was similar, those from the relatively infertile strain had disproportionately larger pituitaries, testes, and combs. Sexual maturity, measured by age at first egg, was consistently earlier for the females of the infertile strain. The larger pituitary of the young males of the infertile strain may provide an excess of gonadotrophic hormones which induce a precocious development of the testes and thus an early development of the comb. Whether or not such changes in these young males are responsible for the relative infertility of their strain remains to be determined.

JACOBSEN, Buffalo.

THE RENAL β-GLUCURONIDASE RESPONSE TO ANDROGENS. WILLIAM H. FISHMAN, M. ARTENSTEIN, and S. GREEN, Endocrinology 57:646-657 (Dec.) 1955.

The mouse renal β-glucuronidase response to androgen is a reproducible phenomenon. The purpose of the present study has been to survey a variety of steroids in order to learn which ones possessed the property of enhancing kidney β-glucuronidase in A/Jax mice under standard conditions. The results obtained in more than 75 compounds are the subject matter of this communication.

Attention has been focused on position 17 of the steroid molecule as a particularly important area in the molecule which has a determining effect on the steroid's potency with regard to the renal β-glucuronidase response. These results are discussed in relation to other renal enzymes and non-sex-organ effects of androgens.

JACOBSEN, Buffalo.

THE DETERMINATION OF FORMALDEHYDOGENIC CORTICOIDS IN GUINEA PIG URINE. A. K. HALAMA, Endocrinology 57:641-645 (Dec.) 1955.

The present investigation was carried out in order to learn if changes of the adrenocortical activity in stress can be evidenced by estimating the urinary excretion of formaldehydogenic corticoids in guinea pigs. Exposure to cold was used as stressor.

A marked rise after prolonged exposure to cold, after injury, and shortly before death was observed. The method used in this investigation proved simple, cheap, and sensitive.

JACOBSEN, Buffalo.

OXYTOCIC ACTIVITY OF DIENCEPHALON AND TUBER CINEREUM OF NORMAL AND HYPOPHYSECTOMIZED RATS. V. SILVA MORENO, H. CROXATTO, N. ALISTE, and O. AMPUERO, Endocrinology 57:658-660 (Dec.) 1955.

The presence of oxytocic, antiduretic, and vasopressor activities has been reported for the hypothalamus. These activities have been identified with corresponding activities of the posterior lobe of the hypophysis. If the hormones are carried from the supraoptic nucleus to the posterior lobe of the hypophysis, the distribution of the active principles should change whenever the connections are severed. In order to study this problem, the author's determined the oxytocic potency of the supraoptic nucleus and of the tuber cinereum region in hypophysectomized rats.

The oxytocic activity of the tuber of hypophysectomized rats was found to be higher than that of control animals.

JACOBSEN, Buffalo.

THE REPORTED INHIBITION OF DCA-SALT HYPERTENSION BY ANTIHISTAMINIC DRUGS: EFFECTS OF SANDOSTENE, PHENERGAN AND CHLORPROMAZINE. G. M. C. MASSON, R. C. NAIRN, and A. C. CORCORAN, Endocrinology 57:670-675 (Dec.) 1955.

Treatment of uninephrectomized rats with desoxycorticosterone acetate (DCA) and salt results in renal, splanchnic, myocardial, and cerebral vascular lesions identical with those of experimental renal hypertension and similar in many respects to the lesions

of hypertensive disease in human beings. The mechanism of formation of these lesions is unknown, except that arterial hypertension seems to be a contributory factor. The importance of increased vascular permeability in this connection seems to have been confirmed by the observations that the administration of drugs which decrease vascular permeability by their strong antihistaminic actions, inhibits both the lesions and the hypertension.

The data presented indicate that Phenergan, Sandostene, and Chlorpromazine, three related compounds of which the first two are antihistaminic, did not protect uninephrectomized rats against hypertension and the cardiovascular lesions consequent on treatment with DCA and salt.

It is suggested that the effects of the antihistaminics and of Chlorpromazine on salt intake may explain the discrepancy, so that apparent protection would be observed whenever the drugs induced a sufficient salt anorexia.

JACOBSEN, Buffalo.

THE EFFECTS OF LOW PRESSURE ON HEMOPOIESIS IN THE ADRENALECTOMIZED RAT. SAM JOSEPH PILIERO, Endocrinology 57:676-682 (Dec.) 1955.

In view of the steadily increasing emphasis being placed on the adrenal gland as a regulator of many phases of body metabolism, a detailed correlation of the peripheral blood changes to the bone-marrow cytology in the adrenal insufficient animal, with and without replacement therapy, was made in an effort to determine the mechanisms underlying the influence of adrenal cortical principles upon the blood elements. It is concluded that, although adrenalectomy in the rat results in alterations in the red cell production and/or destruction mechanisms, the adrenal is not essential for the response to the erythropoietic stress imposed by lowered barometric pressures.

JACOBSEN, Buffalo.

RESPONSES OF OVARIES OF IMMATURE CHICKENS TO AVIAN AND MAMMALIAN GONADOTROPHINS. B. C. DAS and A. V. NALBANDOV, Endocrinology 57:705-710 (Dec.) 1955.

These studies support the idea that there is a qualitative difference between the avian and mammalian gonadotrophic complexes. Whether the avian hypophysis secretes a third gonadotrophic factor, or whether avian FSH or LH have properties not present in their mammalian counterparts, remains to be found.

JACOBSEN, Buffalo.

STUDIES ON THE ROLE OF GROWTH HORMONE IN PREGNANCY. GEORGE H. BEATON, MI HEH RYU, and E. W. MCHENRY, Endocrinology 57:748-754 (Dec.) 1955.

It has been postulated by various workers that growth hormone might play a part in gestation in view of the rapid fetal growth and marked nitrogen retention. Attempts to detect this hormone in the urine of pregnant women and blood of pregnant goats have met with failure.

The data presented in this paper suggest that growth hormone may be responsible for at least some metabolic alterations during pregnancy in the rat.

JACOBSEN, Buffalo.

SELECTION OF PHOSPHORUS IN ALLOXAN DIABETES. ILMARI VARTIAINEN and MATTI PAASONEN, Endocrinology 57:513-515 (November) 1955.

The intake of phosphorus by alloxan diabetic rats was three to five times as great as that of control rats. This seems to point to an increased phosphorus requirement in diabetic rats.

JACOBSEN, Buffalo.

CONGENITAL GALACTOSEMIA; A SINGLE ENZYMATIC BLOCK IN GALACTOSE METABOLISM. K. J. ISSELBACKER, E. P. ANDERSON, K. KURAHASHI, and H. M. KALCKAR, Science 123:635 (April 13) 1956.

In the normal subject the pathway by which ingested galactose is converted to glucose involves four steps, as follows: (1) phosphorylation of galactose to galactose-1-phosphate, involving the enzyme galactokinase, (2) incorporation of Gal-1-PO_4 into a nucleotide, uridyldiphospho-galactose (UDPGal), involving the enzyme PGal-uridyl transferase, (3) conversion of UDPGal to UDPGlucose, through the action of the enzyme galacto-Waldenase,

(4) final release of glucose-1-phosphate from the uridyl complex through the action of a fourth enzyme. The resulting glucose-1-phosphate is then available to enter into reactions culminating in either glycogen or free glucose.

Through a study of erythrocytes from galactosemic subjects, the authors have demonstrated that the enzymatic defect present in this condition is a single one, namely the one concerned with step (2) above, and that the other three enzymes are present in normal amounts.

Patients with galactosemia can therefore be said to be suffering from a congenital lack of enzyme phospho-galacto-uridyl transferase.

FORBES, Rochester, N. Y.

THE NEW ORAL HYPOGLYMIC COMPOUNDS [A Series of Four Articles], Science 123: (April 6 and May 18) 1956.

These articles confirm and extend the observations reported late last year from Germany (*Deutsche med. Wchnschr.* 80:1449, 1452, 1955) to the effect that certain sulfonamide-like compounds possess hypoglycemic activity and show great promise in the treatment of selected patients with diabetes mellitus.

The two compounds which have been principally under study are 1-butyl-3-*p*-tolyl-sulfonylurea (Orinase) and N-*p*-amino-benzene-sulfonyl-N'-N-butylurea BZ-55).

Mirsky and co-workers report that oral doses of Orinase (50 mg/kg.) resulted in a prompt lowering of blood sugar to 20 to 60% of the control level in adult diabetic subjects; very little if any effect was obtained in a group of juvenile diabetics, however.

Miller and Dulin report that Orinase administration lowers blood sugar in rats, dogs, and rabbits and that concomitantly a slight rise in liver glycogen occurs.

Kinsell and co-workers gave these compounds to a group of 10 patients with diabetes. Three obese middle-aged diabetics exhibited a 50% reduction in insulin requirement. Three of five cases of "severe" diabetes also had a decrease; one had an increased need for insulin, and in one there was no change. Of the two juvenile diabetics, one responded favorably while the other had increased glycosuria.

Toxic manifestations noted were (1) marked decrease in radioiodine uptake by the thyroid, (2) moderate decrease in circulating granulocytes, (3) maturation arrest in bone marrow. All of these appeared readily reversible.

M. Vaughan reports experiments aimed at the mode of action of these compounds. Insulinase activity is not inhibited, nor is glucose-6-phosphatase. However, the effect of epinephrine on glucose release from liver slices is markedly diminished.

FORBES, Rochester, N. Y.

HORMONAL TREATMENT FOR THE DYSTROPHIC INFANT. N. C. FERREIRA, F. LOPES, and S. FONSECA, Lattante 26:553 (Sept.) 1955.

In a study made at a hospital in Lisbon, Portugal, 24 dystrophic infants were given 25 mg. methyltestosterone by injection every other day for a period of four weeks. Definite gains in weight and in height were obtained. No further benefit resulted from lengthening the course of treatment to eight weeks or by the giving of twice the dosage (50 mg.). No definite changes in the bones were detected by x-ray films. No virilizing signs were evident, even when the 50 mg. dose was given.

HIGGINS, Boston.

THE EFFECT OF CROUNOTHERAPY ON THE FUNCTION OF THE ADRENAL GLANDS IN CHILDREN. M. L. AMADASI and I. S. SALA, Pediatria 62:884 (Nov.) 1954.

A group of children were given hydrotherapeutic treatments with water containing salts of iodine and bromine. Before and after the course of treatments, the adrenal activity was tested by determinations of the urinary excretion of 17-ketosteroids and 11-oxycorticoids, by eosinophile blood counts, and by sodium and potassium contents in the blood serum. The results indicated that there was no consistent effects of the hydrotherapy on the adrenal function.

HIGGINS, Boston.

Cutaneous Diseases; Allergy

THE SENSITIZATION OF INFANTS TO THE PROTEIN OF COW'S MILK. E. DE TONI and G. R. MITOLO, Lattante 26:562 (Sept.) 1955.

Skin tests for sensitivity to mother's milk were made on 46 infants, 1 to 6 months of age; all were negative. Skin tests for sensitivity to cow's milk were made on a group of 84 infants of the same ages; 12 (14%) were positive; some of the positive tests were obtained in healthy infants who had not had gastrointestinal disorders, but infants with a history of dyspeptic episodes were quite prone to have a positive test. The sensitivity to cow's milk was usually lessened if the amount of milk in the feedings was diminished.

HIGGINS, Boston.

THE EFFECT OF CORTICOTROPIN AND CORTISONE ON RESPIRATORY FUNCTION IN BRONCHIAL ASTHMA. T. W. FYLES, J. A. P. PARE, and BRAM ROSE, J. Allergy 26:340 (July) 1955.

Eight patients, the youngest was 19 years old, the oldest 58 years old, with bronchial asthma, were hospitalized. There was a control period of two weeks during which there was done a complete medical and allergic work-up, including pulmonary function tests. Treatment during this period was limited to symptomatic relief. Corticotropin therapy was started in the hospital. The patients were discharged on oral cortisone, and returned at intervals for repeat pulmonary function tests.

Author's Summary: "The effect of long-term therapy with corticotropin and cortisone on the pulmonary function of eight patients with bronchial asthma has been studied. Four patients showed normal pulmonary function at the end of the study, three were normal with the exception of an elevated residual volume, and one showed no change. In three cases in which the residual volume remained elevated, symptoms of asthma were only incompletely relieved. It was found that there was rapid improvement in the vital capacity, maximum breathing capacity, and index of pulmonary mixing with treatment but the residual volume required somewhat longer periods of therapy to return to normal. It is believed that the changes in pulmonary function found in bronchial asthma are due to hyperinflation of the lungs occassioned by the bronchospasm encountered in this disease and that, with treatment sufficient to completely remove the bronchospasm, these changes are reversible."

HOYER, Cincinnati.

STUDIES IN PENICILLIN HYPERSENSITIVITY: II. THE SIGNIFICANCE OF PENICILLIN AS A CONTAMINANT. MONROE COLEMAN and BERNARD B. SIEGEL, J. Allergy 26:253 (May) 1955.

A detailed case history of a 29-year-old nurse shown to be sensitive to penicillin is reported. She had received penicillin intramuscularly in 1949. She had itching of the skin and throat, urticaria, and angioedema in 1952 following the ingestion of one 200,000-unit penicillin tablet. Similar symptoms together with asthma, vomiting, abdominal pains, and syncope occurred in June, 1953, after an injection of 25 mg. of aqueous suspension of testosterone with a small amount of 1% procaine hydrochloride.

Skin tests to testosterone and procaine were negative; those to penicillin were positive. Subsequent investigations using passive transfer studies revealed minute amounts of penicillin in the syringes used for the injection and the sterilizer in which they were boiled. The water in the sterilizer had not been changed in several months but had been replenished as needed and reboiled. This water produced a positive skin reaction. Likewise sterile water in a syringe contaminated with penicillin produced a positive skin reaction. It was shown that 0.00001 unit of penicillin produced a positive skin reaction. This represents one thirty-billionth of a 300,000 unit dose of penicillin.

Crystalline penicillin G as a contaminant in water gave a positive skin test after 16 hours of boiling.

An important consideration of penicillin contaminated syringes is the need for adequate cleansing of the sterilizer and the syringe.

A possibility arising out of the use of penicillin contaminated syringes for the repeated injection of other medications is that the patient, if a susceptible atopic person, may become sensitized to the antibiotic.

"Recommendations for the prevention of contamination of syringes with penicillin are presented."

HOYER, Cincinnati.

METACORTANDRACIN (PREDNISONE) IN BRONCHIAL ASTHMA COMPARATIVE EFFECTS OF METACORTANDRACIN, HYDROCORTISONE, AND CORTISONE IN BRONCHIAL ASTHMA WITH DIABETES MELLITUS AND BRONCHIAL ASTHMA WITH NASAL POLYPS: PRELIMINARY REPORT. EMANUEL SCHWARTZ, J. Allergy 26:206 (May) 1955.

Metacortandracin was used for 94 days on a patient with severe asthma and diabetes mellitus and for 96 days on a patient with severe asthma and large nasal polyps. Both patients had been on cortisone and hydrocortisone.

In the patient with diabetes mellitus and asthma, glycosuria was less and insulin requirements were lower with metacortandracin than with cortisone or hydrocortisone.

In the patient with nasal polyps and severe asthma, there was greater decrease in the size of the polyps and shrinkage was much more effective with metacortandracin than with cortisone or hydrocortisone.

There were no undesirable side-effects from metacortandracin.

HOYER, Cincinnati.

METACORTANDRACIN IN CHRONIC ASTHMA. JOSEPH SKAGGS, JEROME BERNSTEIN, and ROBERT A. COOKE, J. Allergy 26:201 (May) 1955.

Metacortandracin was used on eight patients who had chronic asthma.

The initial dose was 15 to 50 mg. daily divided into four doses. The dose was modified according to the patients' response.

"From these few cases, it appears that metacortandracin is useful in the treatment of asthma."

There was no evidence of fluid retention, elevation of blood pressure, or glycosuria. None of these patients had been on the drug for more than a month.

HOYER, Cincinnati.

METICORTEN AND 9 ALPHA FLUOROHYDROCORTISONE IN THE TREATMENT OF ALLERGIC DISORDERS. CARL E. ARBESMAN, and ROBERT J. EHRENREICH, J. Allergy 26:189 (May) 1955.

Seven patients with severe asthma were given 1 mg. 9α-fluorohydrocortisone for each 25-mg. tablet of cortisone or 20-mg. tablet of hydrocortisone which had been used previously in their treatment. The new steroid has little value in the relief of bronchial asthma. It does have powerful sodium-retaining properties.

Meticorten (metacortandracin) was given to 20 patients; 17 had been on cortisone, hydrocortisone, or 9α-fluorohydrocortisone, and 3 had not had any steroid. The drug was given in four divided doses daily, 5 mg. for each 25-mg. tablet of cortisone, or 20-mg. tablet of hydrocortisone. The dosage was then reduced to a minimum which would give symptomatic relief.

Beneficial results were obtained in 15 asthmatic patients who had obtained relief with other steroids. One asthmatic who had had no steroids previously was much improved.

A patient with dermatomyositis did better with Meticorten than with hydrocortisone. A patient with severe allergic rhinitis and another with urticaria and angioneurotic edema were not benefited.

Meticorten in the dosages used did not affect sodium or potassium metabolism, the body weight, or blood pressure. Meticorten is four to five times as effective as cortisone or hydrocortisone. It is not a substitute for the specific management of the allergic patient.

HOYER, Cincinnati.

CAMAZULENE IN ALLERGY; TESTS IN CASES OF ASTHMA AND INFANTILE ECZEMA. G. R. MITOLO, Minerva pediat. 6:988 (Dec. 31) 1954.

No clinical benefit could be observed after the giving of Camazulene to 11 children with asthma and to 6 children with eczema. This drug, the active ingredient of camomile, had previously been found not to protect guinea pigs from anaphylactic shock.

HIGGINS, Boston.

Teeth and Dentistry

FLUORIDATION PART III. F. B. EXNER, Northwest Med. 54:1255 (Nov.) 1955.

Part III of a three-part discussion of fluoridation by an outspoken opponent of fluoridation of public water supplies discusses possible basic motives of proponents. Pointing his

guns at the Public Health Service, the author gives many reasons for concluding that fluoridation of public water supplies is not to be recommended.

DOCTER, Seattle.

TRANSPLANTATION OF TOOTH BUDS. W. BEJDL and J. WEIZENBERG, Wien. klin. Wchnschr. 67:577 (Aug. 12) 1955.

Tooth buds were taken from rats and rabbits, 3, 7, and 14 days of age, and transplanted into muscle pockets or subcutaneously into adult animals. Transplants were made and developed in 25 days to a normal tooth.

from rat to rat, rabbit, and guinea pigs, or from rabbit to rat. Buds taken from 3-day-old animals developed within a month to a small tooth. Buds taken on the 7th day developed within 23 days to a tooth of normal size; buds taken on the 14th day were further advanced

AMBERG, Rochester, Minn.

INFERIOR GNATOCHIESIS. E. R. VIRGIL LORENZO, Rev. españ. pediat. 11:93 (Jan.-Feb.) 1955.

The author presents a case history of a gross malformation in an infant involving a split of the lower jaw including the floor of the mouth, the tongue, and extending to the neck. The upper part of the face was undeformed. The child was one of twins. Despite efforts at feeding in preparation for repair, the child died of aspiration pneumonia on the 10th day.

The mother, whose first pregnancy this was, gave no history of viral infection in early months of pregnancy. Both parents were young and well. However, the next pregnancy after this one produced a child with multiple defects, none of which were incompatible with life. The third pregnancy terminated in an unexplained abortion. The author believes the defect is genetic in origin.

ALLEN, Santa Fe, N. M.

THE CONCURRENCE OF LIP AND HARD AND SOFT PALATE CLEFTS WITH MALFORMATIONS OF THE EXTREMITIES. H. SCHÖNENBERG, Ztsch. Kinderh. 76:79, 1955.

The author demonstrates the frequent combination of cleft palates and harelips with malformations of the extremities by reviewing six cases of his own observation and references in the literature.

Etiologically it is considered an arrest in development occurring before the ninth week of pregnancy which also explains the frequent association with cerebral malformations, as demonstrated in three cases by pneumoencephalogram.

GLASER, Baltimore.

News and Comment

ANNOUNCEMENTS

Change of Title and Coverage.—The Council of Biological and Medical Abstracts Ltd. has decided to change the title of their journal *British Abstracts of Medical Sciences* to *International Abstracts of Biological Sciences.*

This decision results from two major developments. The first is an extension of coverage to a wider range of biological research subjects published in journals throughout the world, and the second is that the International Abstracts of Biological Sciences, with the co-operation of the specialist editors selected by the Institute of Scientific Information of the Academy of Sciences of the U. S. S. R. will include, as from the January 1957 issue, translations of the important Russian papers abstracted in the *Referativny Zhurnal Biologii* (Soviet Biological Abstracts) and *Referativny Zhurnal Biologischekoi Khimii* (Soviet Abstracts of Biological Chemistry), to be published simultaneously with their appearance in Russian.

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Kenny Foundation Scholarship Program.—The Sister Elizabeth Kenny Foundation announces a program of post-doctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

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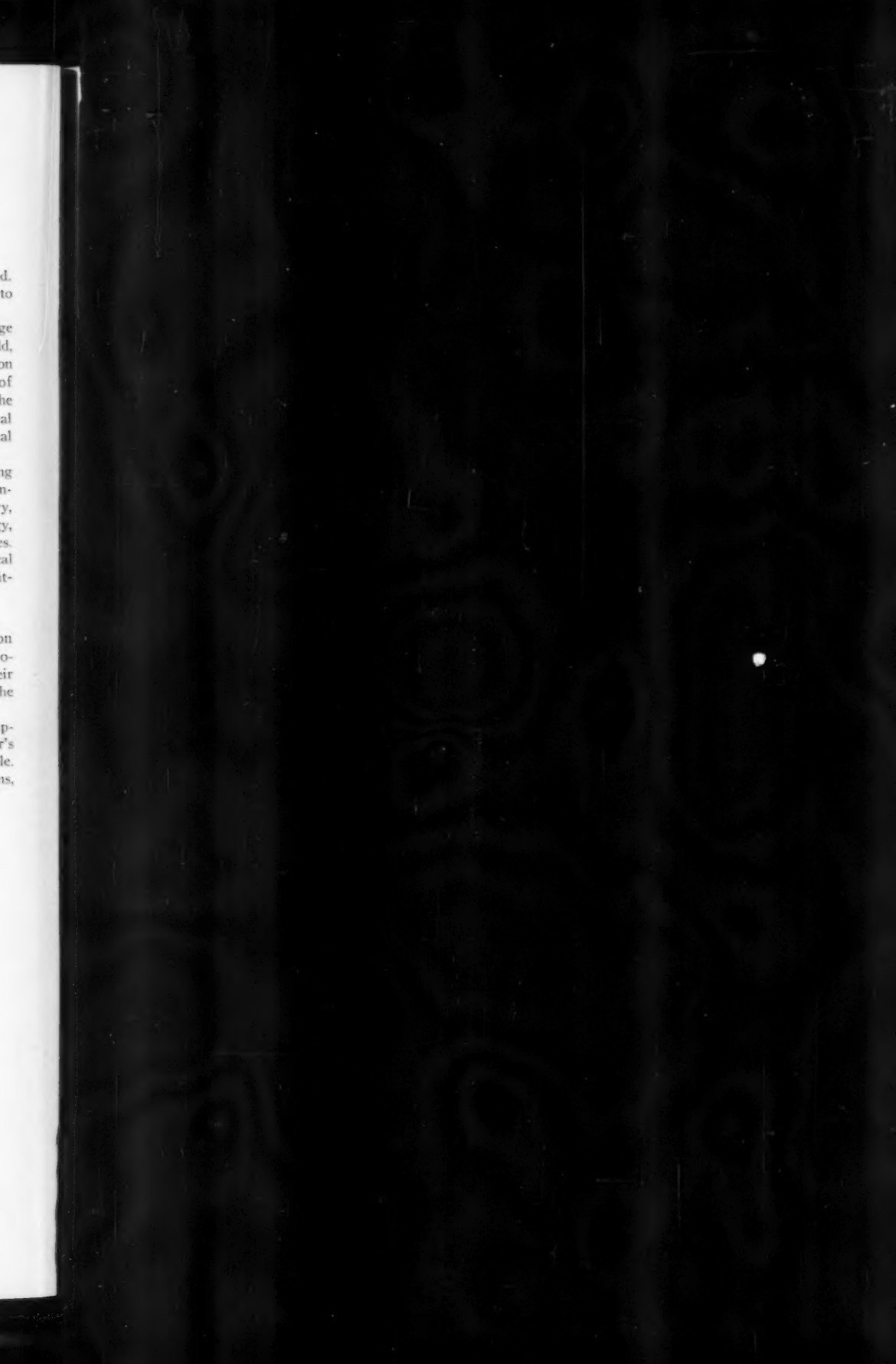

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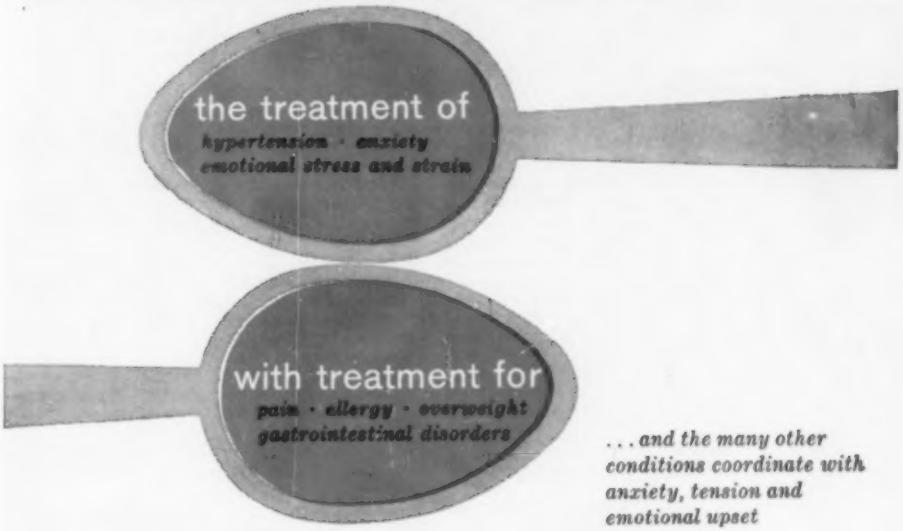

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which can
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and shorten
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1. Johnson, S. H., III, and Marshall, M., Jr.: A. M. A. Am. J. Dis. Child. 89:199, 1955.
2. Breakey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. 54:805, 1955.

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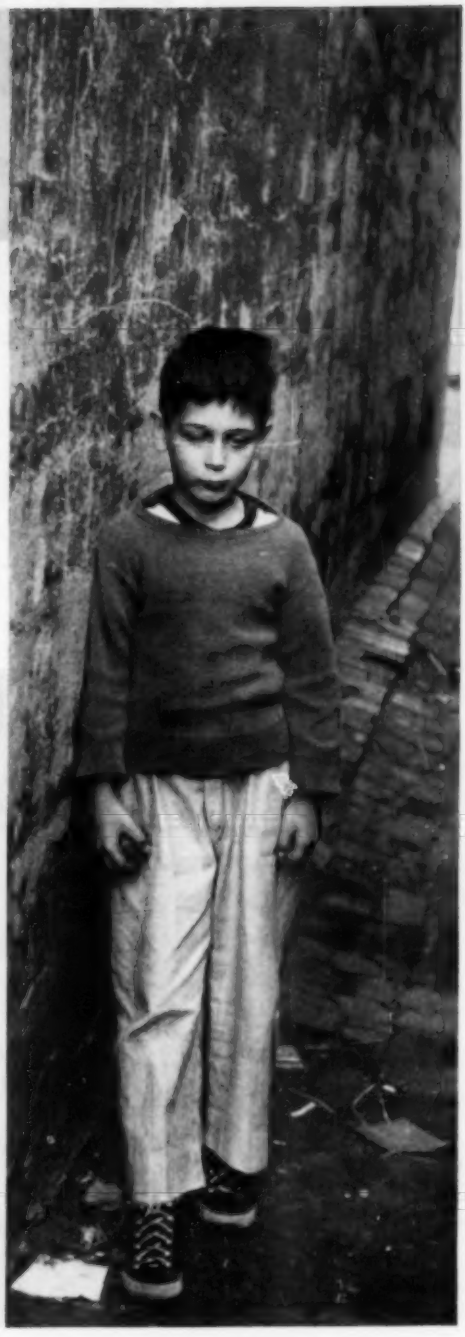

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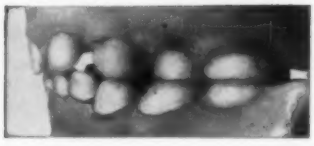
since infancy caused this 4 year old's malocclusion.



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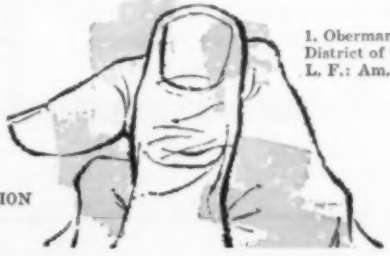

1. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954. 2. Hill, L. F.: Am. J. Clin. Nutrition 3:75, 1955.

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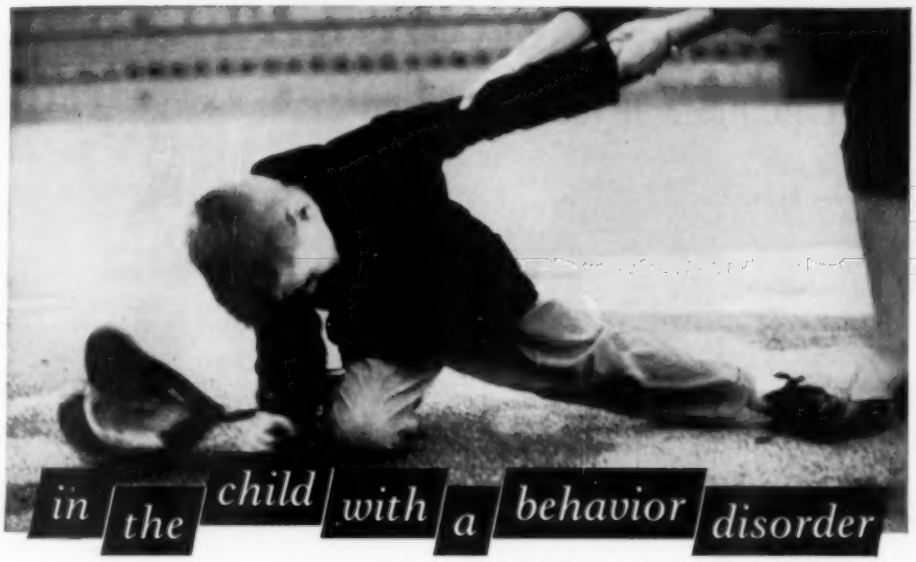

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reduces hyperactivity and aggressiveness

decreases anxiety and hostility

improves mood, behavior and sleeping habits

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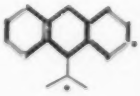

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in infants and young children

Colace

DIOCTYL SODIUM SULFOSUCCINATE, MEAD JOHNSON*

softens stools for easy passage

without laxative action • without adding bulk

"Instead of juggling the formula and trying a multitude of colic remedies, laxatives, suppositories, malts, high syrup or sugar additions, the simple procedure of adding a few drops of...[Colace Liquid] to the formula literally works a miracle."†

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0 to 3 years.....10 to 40 mg.
3 to 6 years.....20 to 60 mg.
6 to 12 years.....40 to 120 mg.

‡Colace may be given in divided doses. The higher dosage is recommended during initial phase of therapy. Dosage should be adjusted as required by individual response.

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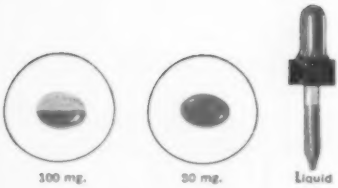
Colace Liquid (1% Solution: 1cc.=10 mg.), 30 cc. bottles with calibrated dropper. To mask the bitter taste, administer in half a glass of milk or fruit juice, or in formula. Colace Capsules 50 mg., bottles of 30, 60 and 250. New Colace Capsules 100 mg., bottles of 30, 60 and 250.



†Antos, R. J.: A New Approach to the Treatment of Severe Constipation, Southwestern Med. 37:236, 1956.

*Patents pending

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SECOND—Varamel is fortified with sufficient pure synthetic vitamins to provide the daily recommended allowance of all known essential vitamins.

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FOURTH—Iron is added to supply 7.5 milligrams per quart of formula.

FIFTH—Varamel contains only the sugar from the milk used, so the physician can add the necessary amount of carbohydrate to meet the nutritional needs of the infant.

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Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.8

Calories per fl. oz., 32

*Made from Grade A Milk (U. S. Public Health Service Milk Code)

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